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IN VITRO ACTIVITY OF VARIOUS PENICILLINS*

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Among the great hopes for the development of more useful antimicrobial agents is the prospect of synthesizing new ones to fit predetermined specifications. Before this becomes a reality, however, it will be essential to acquire the necessary background of information concerning the effects that progressive changes in chemical structure of agents with known activities have on the important biological properties for which they are selected, and on any undesirable ones they may produce which must also be considered in using them. The isolation of 6-aminopenicillanic acid (6APA) from penicillin fermentations (Batchelor *et al.*[3]) has provided a useful chemical intermediate for the preparation of new penicillins and related compounds which could not easily be prepared by adding appropriate precursors to the fermentation media. Certain of these penicillins have properties which, according to

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one of their developers (Rolinson[21]), give promise of some very useful applications.

The first of these new penicillins to be exploited for therapeutic purposes is 6(α-phenoxypropionamido) penicillate, or phenoxyethylpenicillin, which has been given various trade names* but now has the generic designation phenethicillin. Elsewhere[18,19] we have reported observations on the antibacterial activity produced in serum after oral doses of this new compound as compared with that resulting from equivalent doses of other penicillins. These studies, and others reported by Griffith[12], indicated that the much better absorption and higher serum levels reported for oral phenethicillin as compared with oral penicillin V or intramuscular penicillin G by other workers (Cronk *et al.*[7], Knudsen and Rolinson[17], Morigi, Wheatley and Albright[20]) are not accompanied by greater antibacterial activity in the serum against certain pathogenic organisms (*Staphylococcus aureus, Streptococcus hemolyticus* and type 3 pneumococcus), or when compared with a single standard penicillin, namely penicillin G. This discrepancy was shown to be due to differences in the susceptibility of the assay organisms to the different penicillins (McCarthy and Finland[18]). Inasmuch as antibiotics are used specifically for their effects against the causative organisms of infections, it is important to compare the activity of the different penicillins against a large number and variety of pathogens. This paper presents the results of *in vitro* tests of the susceptibility of such pathogens to several penicillins, including the stereoisomers of phenethicillin, and to the related synnematin B (cephalosporin N) (Abraham and Newton *et al.*[1,2], Heatley and Florey[13], Jackson, Rubenis and Mellody[15]). Similar observations of more limited scope have already been reported by others (Garrod[8], Gourevitch, Hunt and Lein[10], Griffith, Ostrander and Smith[11]).

Materials and Methods. The penicillins used in this study, their suppliers, and the symbols used for convenience to refer to them in this paper are listed in Table 1. Freshly prepared solutions containing the acid equivalent of 4 or 8 mg. per ml. in distilled water were distributed into tubes which were kept frozen until used, generally within 2 to 6 weeks, and were not refrozen after they had been thawed. The great majority of the bacterial strains were recently isolated from clinical materials routinely submitted for culture in the Bacteriology Laboratory of the Mallory Institute of Pathology and identified by Miss A. Kathleen Daly and Miss Alice McDonald of that laboratory. The streptococci were "grouped" by Dr. Harry A. Feldman of the Upstate Medical School, Syracuse, N.Y., who also provided a number of these strains. Some of the pathogenic types of *E. coli* and of Klebsiella and Aerobacter were obtained from Dr. P. R. Edwards, Communicable Disease Center, Atlanta, Georgia.

The tests for susceptibility were carried out, for the most part, on appropriate solid media into which 2-fold dilutions of the antibiotics were incorporated, the great majority being done by the replicate mechanical method of Steers, Foltz and Graves[22]; duplicate tests of some groups of strains were carried out in parallel by the usual method of streaking on segments of plates with a 1 mm. bacteriological loop. In each of these methods the inoculum contained approximately 10^6 viable organisms obtained directly from a fully grown culture that had been incubated at 37° C. overnight. A few comparative tests were also done with two-fold dilutions of antibiotic in liquid media using an inoculum that provided approximately 10^5 organisms per ml. obtained from similar cultures. Defibrinated horse blood was used in the media for growth of streptococci and pneumococci, and "chocolate" agar or broth was used for strains of Hemophilus and Neisseria and these were incubated under increased CO_2 tension. The minimum inhibiting concentration (MIC) was taken to be that concentration of

*Broxil (Beecham), Syncillin (Bristol), Maxipen (Roerig), Alpen (Schering), Chemipen (Squibb), Dramacillin (White), and Darcil (Wyeth); also the laboratory designations P152 (Beecham), P152DL (Bristol) and PA228 (Pfizer).

antibiotic which produced no growth or only minimal growth discernible only with the aid of a hand lens; this was expressed in μg. per ml. of the free acid. Groups of strains of the same or related species were tested with the different penicillins at the same time.

REPRODUCIBILITY OF TESTS. In order to control the reproducibility of the results of the tests on different days and also to maintain a control of the stability of the solutions of antibiotics as they were being kept in the frozen state after they were prepared, one or more standard laboratory strains were included with each test of a group of organisms. With rare exceptions, the MIC of each of the penicillins for each of these standard strains varied within a single two-fold dilution from the mean of all tests with that strain. The results of all these tests are summarized in Table 2.

COMPARISON OF RESULTS OF TESTS DONE BY DIFFERENT METHODS. In 688 direct comparisons of simultaneous tests with individual strains carried out by the mechanical replicator and the plate dilution method employing a loop for the inoculations, with the same undiluted cultures and the same solutions of the various penicillins, the two methods gave very similar results. In 28% of these tests the endpoints were identical, in 35% the MIC obtained with the mechanical method was greater, and in 37% the MIC was greater when the plates were streaked with the loop. The differences were usually only a single two-fold dilution, and less than 5% of the tests gave greater (four-fold) differences. On the other hand, in 108 comparisons of the mechanical and tube-dilution methods, the former gave higher endpoints than simultaneously performed tube-dilution tests in over 80% of such comparisons and the mean and

TABLE 1.—PENICILLINS USED IN THIS STUDY

*Type of Penicillin**	*Symbol†*	*Supplier(s)*
benzyl penicillin	G	Squibb
phenoxymethyl pencillin	V	Lilly & Pfizer
D-phenoxyethyl pencillin†	D	Bristol
L-phenoxyethyl pencillin†	L	Bristol
DL-phenoxyethyl pencillin‡	DL	Bristol & Pfizer
phenylmercaptomethyl penicillin	PM	Lilly
·ynnematin B	SB	MDHL§

*Each supplied as sterile powders of the potassium salt, except SB, which was supplied as the free acid; all concentrations, however, are expressed as acid equivalents throughout this paper.
†Used for convenience in charts, tables and text; only G and V are generally accepted designations.
‡6-(α-propionamido) penicillanate; the DL-stereoisomer has been given the generic name phenethicillin; the preparations used contained about 65% L and 35% D forms.
§Michigan Department of Health Laboratory.

TABLE 2.—SUMMARY OF RESULTS OF REPEATED TESTS DONE AT DIFFERENT TIMES WITH THREE STRAINS USED AS CONTROLS DURING THESE STUDIES

	Staphylococcus 209P		*Streptococcus 98*		*Sarcina lutea*	
*Penicillin**	*No. of Tests*	*MIC†*	*No. of Tests*	*MIC†*	*No. of Tests*	*MIC†*
G	16	0.035 ± 0.012	15	0.011 ± 0.008	5	0.004 ± 0.001
V (Lilly)	16	0.034 ± 0.017	15	0.015 ± 0.008	5	0.024 ± 0.010
V (Pfizer)	7	0.044 ± 0.035	12	0.032 ± 0.011	5	0.036 ± 0.010
DL (PA228)	6	0.050 ± 0.038	14	0.031 ± 0.013	5	0.030 ± 0.006
DL (P152)	16	0.093 ± 0.072	15	0.028 ± 0.021	5	0.015 ± 0.009
L	5	0.080 ± 0.086	15	0.020 ± 0.008	5	0.009 ± 0.003
D	6	0.152 ± 0.129	15	0.043 ± 0.048	5	0.024 ± 0.031
PM	14	0.035 ± 0.032	14	0.012 ± 0.011	5	0.006 ± 0.005
SB	5	14.0 ± 9.0	15	10.0 ± 12.0	5	1.44 ± 1.11

*See Table 1.
†Minimum inhibiting concentration, mean ± SD.

TABLE 3.—SUSCEPTIBILITY OF BACTERIA TO VARIOUS PENICILLINS

Organism	*Number of Strains*[a]	*M.I.C. of G-, μg./ml.*	*Ratio of Minimum Inhibiting Concentrations*[b]						
			V/G	*D/G*	*L/G*	*DL/G*	*PM/G*	*SB/G*	*DL/V*
Staphylococcus aureus, S[c]	55	0.02–0.04	$\frac{1}{2}$–2	1–8	1–2	1–2	$\frac{1}{4}$–1	256–512	1–2
		0.03(0.02)	0.9(1)	3.5(4)	1.2(1)	1.3(1)	0.6($\frac{1}{2}$)	315(512)	1.4(1)
Staphylococcus aureus, R[c]	54	1.25–>100	$\frac{1}{2}$–1	$\frac{1}{16}$–1	$\frac{1}{64}$–1	$\frac{1}{32}$–1	$\frac{1}{8}$–1	>100[d]	$\frac{1}{16}$–1
		>100	0.9(1)	0.4($\frac{1}{4}$)	0.21($\frac{1}{8}$)	0.25($\frac{1}{4}$)	0.7(1)		0.28($\frac{1}{4}$)
Streptococcus, group A	85	0.0025–0.2	$\frac{1}{2}$–16	$\frac{1}{8}$–64	$\frac{1}{4}$–8	$\frac{1}{4}$–32	$\frac{1}{16}$–16	256–8192	$\frac{1}{8}$–32
		0.02(0.005)	1.2(2)	5.7(8)	2.0(2)	2.7(4)	0.8(1)	590(512)	2.3(1)
	29[e]"L"	0.0025–0.1	1–32	$\frac{1}{2}$–16	$\frac{1}{2}$–16	$\frac{1}{2}$–16	$\frac{1}{8}$–4	64–8192	$\frac{1}{4}$–2
		0.014(0.005)	7(8)	2.7(2)	4.0(4)	4.3(4)	1.1(1)	725(1024)	0.6($\frac{1}{2}$)
	6"B"	0.005–0.01	$\frac{1}{4}$–1	2–4	1–2	1–4	$\frac{1}{4}$–$\frac{1}{2}$	128–512	2–8
		0.009(0.01)	0.6($\frac{1}{2}$)	2.3(2)	1.1(1)	1.5(1)	0.4($\frac{1}{2}$)	215(256)	2.1(2)
Streptococcus, group B	19	0.005–0.04	$\frac{1}{2}$–8	2–128	1–4	1–16	$\frac{1}{2}$–2	64–512	$\frac{1}{4}$–8
		0.03(0.02)	1.7(2)	13(16)	1.1(2)	2.3(2)	0.6(1)	256(256)	1.4(2)
Streptococcus, group C	6	0.0025–0.2	$\frac{1}{2}$–4	16–256	1–4	1–32	$\frac{1}{2}$–1	128–1024	1–16
		0.04(0.005)	1.5(2)	52(64)	20(2)	9.0(8)	0.6(1)	512(512)	6(4)
Streptococcus, group G	7	0.005–0.04	$\frac{1}{2}$–4	4–64	$\frac{1}{2}$–4	1–32	$\frac{1}{2}$–2	64–512	1–8
		0.02(0.02)	1.2(1)	19(16)	1.2(2)	4.3(4)	1.0(1)	384(512)	3.6(4)
Streptococcus viridans	35	0.0025–0.2	1–4	2–64	1–8	$\frac{1}{2}$–4	$\frac{1}{4}$–2	32–2048	$\frac{1}{4}$–4
		0.05(0.04)	1.3(1)	5.1(4)	1.9(2)	1.6(2)	1.0(1)	315(256)	1.2(2)
Enterococcus, (strep., group D)	43	1.6–3.1	$\frac{1}{2}$–2	4–8	1–2	2–4	$\frac{1}{2}$–2	>100[d]	1–4
		3.0(3.1)	1.3(1)	7.8(8)	1.3(2)	2.8(4)	1.4(1)		2.5(2)
Diplococcus pneumoniae	29	0.01–0.1	$\frac{1}{4}$–2	$\frac{1}{2}$–4	$\frac{1}{2}$–2	$\frac{1}{2}$–4	$\frac{1}{4}$–1	16–256	1–4
		0.04(0.04)	0.5($\frac{1}{2}$)	1.0(1)	0.7($\frac{1}{2}$)	1.4(1)	0.3($\frac{1}{4}$)	52(64)	3.0(2)
Neisseria gonorrhoeae	29	0.005–0.4	$\frac{1}{4}$–8	$\frac{1}{2}$–8	2–32	1–64	1–8	4–256	$\frac{1}{2}$–32
		0.08(0.02)	2.4(4)	3.2(4)	13(16)	6(8)	3.1(2)	48(64)	2.4(2)
	17"L"	0.005–0.2	1–8	2–8	4–32	1–32	$\frac{1}{4}$–8	4–32	1–8
		0.08(0.04)	2.7(4)	4.6(4)	14(16)	6(8)	2.2(4)	16(16)	2.1(4)
	12"B"	0.001–0.04	2–4			1–16	1–4		$\frac{1}{2}$–8
		0.013(0.005)	3.0(4)			6.0(8)	2.7(4)		2.0(2)
Neisseria meningitidis	8	0.02–0.2	4–16	4–16	16–64	8–64	2–8	4–32	2–8
		0.14(0.2)	8(8)	10(8)	30(32)	18(16)	5.3(4)	9.2(4)	2.3(4)
Listeria monocytogenes	2	0.4	$\frac{1}{2}$	2	$\frac{1}{4}$	$\frac{1}{4}$–2	$\frac{1}{4}$	16	1–2

Hemophilus influenzae	25	0.4–6.3 2.0(1.6)	2–16 8(9)	2–32 12(16)	2–64 10(8)	2–16 8(8)	$\frac{1}{4}$–8 1.1(1)	4–128 20(32)	$\frac{1}{2}$–2 1.0(1)
	12"L"	0.4–3.1 1.3(0.8)	4–16 8(8)			8–32 30(32)	2–8 2.7(4)		2–8 3.7(4)
	8"B"	0.2–0.4 0.3(0.4)	4–16 7(8)			8–32 16(16)	$\frac{1}{4}$–4 1.5(2)		1–4 2(2)
Hemophilus, sp.	8	25–>100 50(50)	$\frac{1}{4}$–2 1.0(1)	$\frac{1}{2}$–4 2.0(2)	1–4 2.0(2)	1–2 1.5(2)	1–4 2.2(2)	>100[d]	1–8 1.5(1)
Pasteurella multocida	6	1.6 1.6	$\frac{1}{8}$–$\frac{1}{4}$ 0.17($\frac{1}{6}$)	1 1	2 2	$\frac{1}{2}$–8 2(2)	$\frac{1}{8}$–$\frac{1}{4}$ 0.1($\frac{1}{6}$)		8–32 16(16)
Mima polymorpha	4	0.4–6.3 2.2(1.6)	$\frac{1}{2}$–4 1.8(2)	2–8 4.0(4)	4–8 4.3(4)	2–8 32(4).	$\frac{1}{2}$–1 0.8(1)	2–16 9(16)	$\frac{1}{2}$–8 2(2)
Salmonella	7	50–100 75(100)	1–4 2(2)	>400[d]	>400[d]	>400[d]	1–4 2(1)	$\frac{1}{8}$–8 0.5($\frac{1}{2}$)	>2–>8 >4
Shigella	16	100–200 187(200)	1–2 1.5(2)	2–>4 >4	4–>4 >4	2–>4 >4	1–4 2.0(2)	1–2 1.0(1)	>2 >2
Escherichia coli[e]	19	200–400 250(200)	1–2 1.6(2)	>400[d]	>400[d]	>400[d]	1–2 1.9(2)	$\frac{1}{2}$–2 1.5(2)	>2 >2
Klebsiella pneumoniae	16	all grew in 400 μg/ml except one strain of type A[f]							
Aerobacter[g]	19	all grew uninhibited in 400 μg/ml.							
Herellia sp.	21	all grew uninhibited in 400 μg/ml.							
Proteus	20	all uninhibited by 400 μg/ml, with some exceptions[h]							
Pseudomonas aeruginosa	19	all grew uninhibited in 400 μg/ml.							

Abbreviations for types of penicillins: G = benzyl; V = phenoxymethyl; D = D-phenoxyethyl; L = L-phenoxyethyl; DL = DL-phenoxyethyl; PM = phenylmercaptomethyl; SB = synnematin B.

Footnotes: (a) all tested by method employing the replicating apparatus of Steers, Foltz and Graves,[22] except those followed by "L" which were streaked with a loop on solid media, and those followed by "B" which were tested in broth.

(b) M.I.C.—minimum inhibiting concentration. The upper line for each organism indicates the range, the lower indicates the geometric mean followed in parentheses, by the median; when only one is given the mean and median were the same; the ranges, geometrical means and medians, of the ratios are similarly disposed.

(c) S = sensitive (non-penicillinase producers); R = resistant (penicillinase producers).

(d) Growth of all strains in highest concentration tested

(e) Includes 6 of serotype 022BG; 5 of 055B5; 4 of 086B7 and 3 of 011B4.

(f) M.I.C.'s: G = 50; V = 100; D = >400; L = 400; DL = 400; PM = 50; SB = 25.

(g) *A. aerogenes* 16, *A. cloacae* 3.

(h) 7 strains inhibited by 200 or 400 μg. per ml. of G, and 5 of these were inhibited by 100 or 200 μg. per ml. of SB.

median ratio was 4; that is, the MIC was 4 times greater in the tests done on agar than in those done in liquid media. In all these comparisons, the relative susceptibility of each strain to the different penicillins was essentially the same in each of the tests.

Results. A total of 552 strains of some 20 species or genera of pathogenic bacteria were tested in comparisons using the mechanical replicating method and, in addition, 84 of the strains were tested by either the streak-plate or the broth dilution method. All the penicillins listed in Table 1 were used in tests of groups of strains of the same species or genus at the same time, except for 32 strains that were tested only with G, V, DL and PM, using only one of the preparations of V and DL in these tests, whereas both were used in the tests of all the other strains.

Table 3 summarizes for each species or genus the range, geometric mean and the median of the MIC's of penicillin G for all strains tested. In separate columns are listed the range, geometric mean and the median of the ratio of the MIC's of each of the other penicillins to that of G for the same strains. This type of presentation was considered necessary in order to minimize the amount of tabular material and yet provide a maximum of useful information which permits comparisons of all the penicillins studied against the various organisms tested. The actual inhibiting concentrations will be shown graphically for all the strains of some of the more important species in presenting the results below. However, a direct comparison of DL and V is shown separately in the last column of Table 3, as the ratio of the MICs of these 2 penicillins, because of the special interest in their relative activity. Inspection of Table 3 shows that the relative activity of the different penicillins varied markedly with the different species or genera. The results will, therefore, be described separately for each group of organisms.

Staphylococcus aureus. The relative activity of the various penicillins against these organisms depended on whether or not the strains produced penicillinase. Both the producers and the nonproducers of penicillinase were as susceptible or slightly more so to V and PM as to G. The phenethicillins, on the other hand, were more active than G against the penicillinase producers but they were either as active as G or slightly less so against the nonpenicillinase producers. Among the phenethicillins, the L-isomer was the most active, the D-isomer the least active and the activity of the DL form was intermediate, but more nearly approached that of the L form. SB failed to inhibit any of the penicillinase producers in the highest concentration used, but inhibited all the nonpenicillinase producers in concentrations of 6.3 or 12.5 μg. per ml. The actual and relative activity of these penicillins is shown graphically for the nonpenicillinase producers in Fig. 1. From this figure and from Table 3 it is seen that the order of activity for the great majority of these strains, from the most to the least active, was: PM > V $\geq$ G > L $\leq$ DL > D > SB. The corresponding order of activity against the penicillinase producers, as shown in Fig. 2, was: L = DL > D > V >G $\geq$ PM > SB. More detailed comparisons of the action of these penicillins against penicillinase producers, and particularly the effect of inoculum size, are left for separate consideration elsewhere (Wallmark and Finland[23]).

Streptococcus hemolyticus. The results of tests done by the mechanical replicating method on 85 strains of group A and on smaller numbers of groups B, C and G streptococci showed the relative activity of the dif-

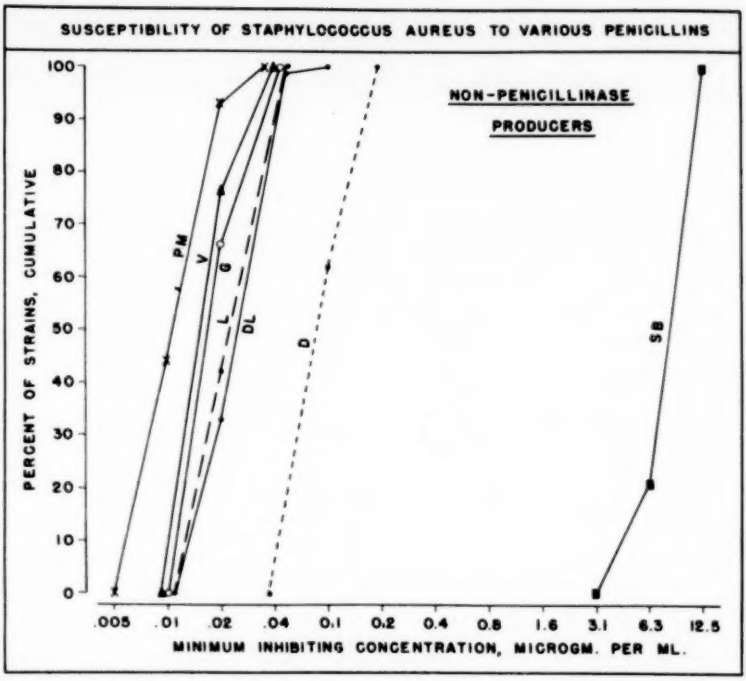

Fig. 1.—The curves in Figs. 1 to 8 inclusive are each based on all tests done with the indicated penicillin: G = benzyl penicillin (open circles connected by solid lines); V = phenoxymethyl penicillin (solid triangles connected by solid lines); PM = phenylmercaptomethyl penicillin (X crosses connected by solid lines): DL = phenoxyethyl penicillin, a mixture of D- and L-isomers (dots connected by solid lines); L = the L-isomer of phenoxyethyl penicillin (dots connected by coarsely broken line; D = the D-isomer of phenoxyethyl penicillin (dots connected by finely broken lines), and SB = synnematin B (solid squares connected by solid lines).

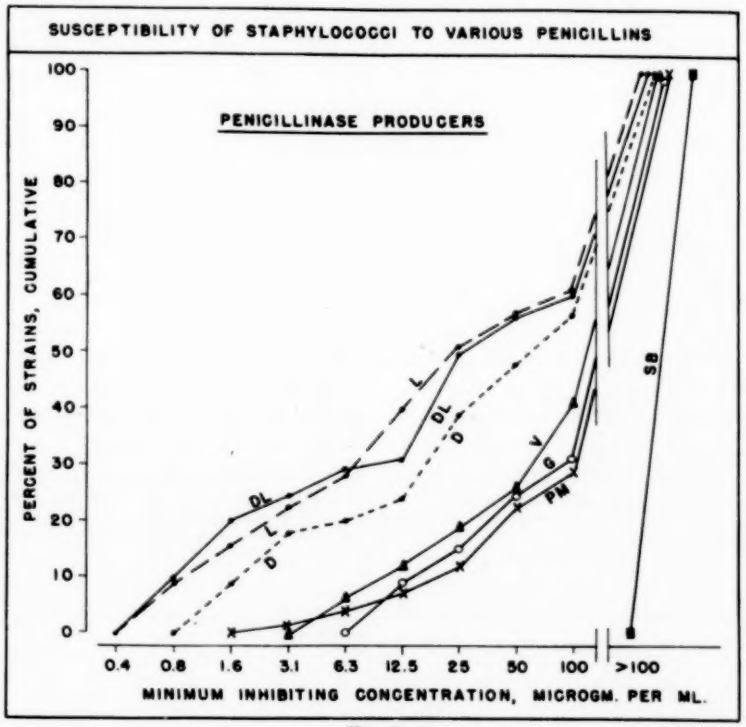

Fig. 2

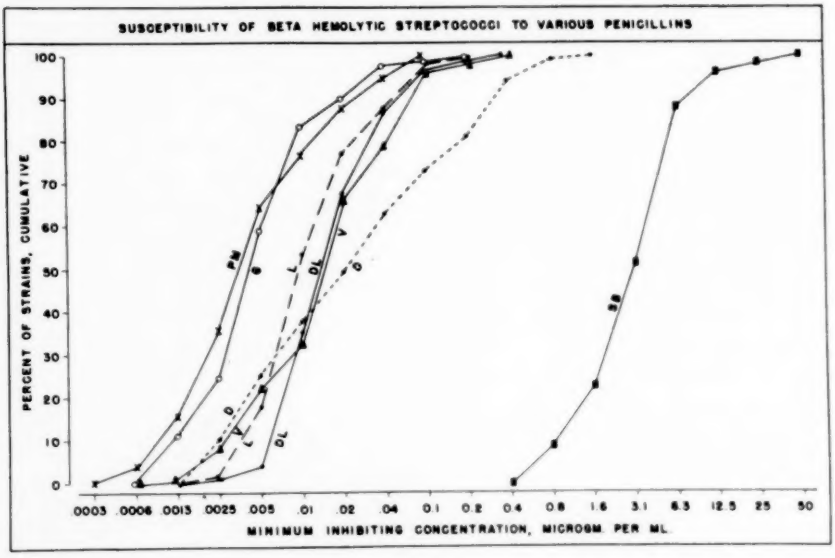
SUSCEPTIBILITY OF BETA HEMOLYTIC STREPTOCOCCI TO VARIOUS PENICILLINS
PERCENT OF STRAINS, CUMULATIVE
100
90
80
70
60
50
40
30
20
10
0
PM
G
V
DL
L
D
SS
.0003 .0006 .0013 .0025 .005 .01 .02 .04 0.1 0.2 0.4 0.8 1.6 3.1 6.3 12.5 25 50
MINIMUM INHIBITING CONCENTRATION, MICROGM. PER ML.

Fig. 3

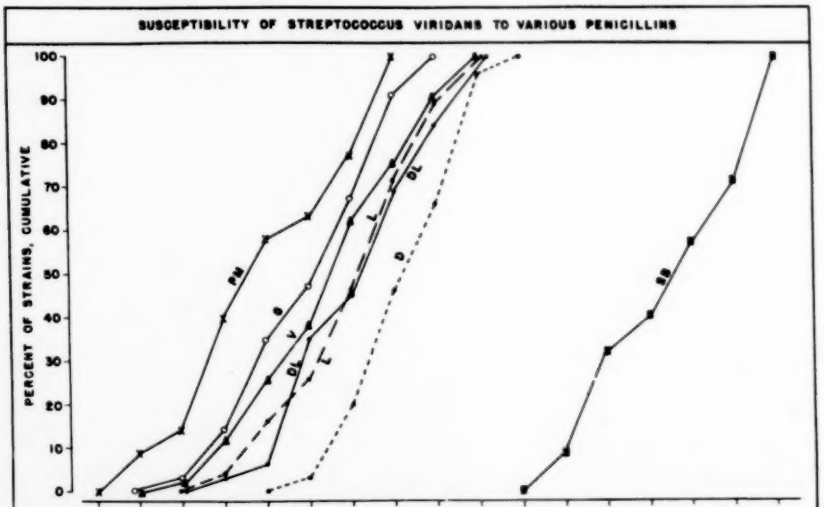
SUSCEPTIBILITY OF STREPTOCOCCUS VIRIDANS TO VARIOUS PENICILLINS
PERCENT OF STRAINS, CUMULATIVE
100
90
80
70
60
50
40
30
20
10
0
PM
G
V
DL
L
D
SS
.0006 .001 .002 .005 .01 .02 .04 0.1 0.2 0.4 0.8 1.6 3.1 6.3 12.5 25 50
MINIMUM INHIBITING CONCENTRATION, MICROGRAMS PER ML.

Fig. 4

ferent penicillins to be similar against these groups except for the D-phenethicillin which was relatively much more active against the group A strains than against those of the other groups. Only PM was generally as active as penicillin G, or more so against nearly all strains. There were wide variations in the relative activity of the other penicillins; this may account, in part, for the discrepancies in the results obtained with group A strains when tested by the different methods. The results of all the tests on the strains of the 4 groups combined are shown in Fig. 3. From this figure it is seen that the order of activity of the different penicillins against the majority of these strains was: PM $\geq$ G > L > DL $\geq$ V > D > SB. The last of these inhibited nearly all of the strains in concentrations of 0.8 to 25 μg. per ml.

Streptococcus viridans. Both alpha hemolytic and gamma streptococci were included. From Table 3 and Fig. 4, the relative activity of the penicillins against most of these strains was: PM > G > V $\geq$ L = DL > D > SB.

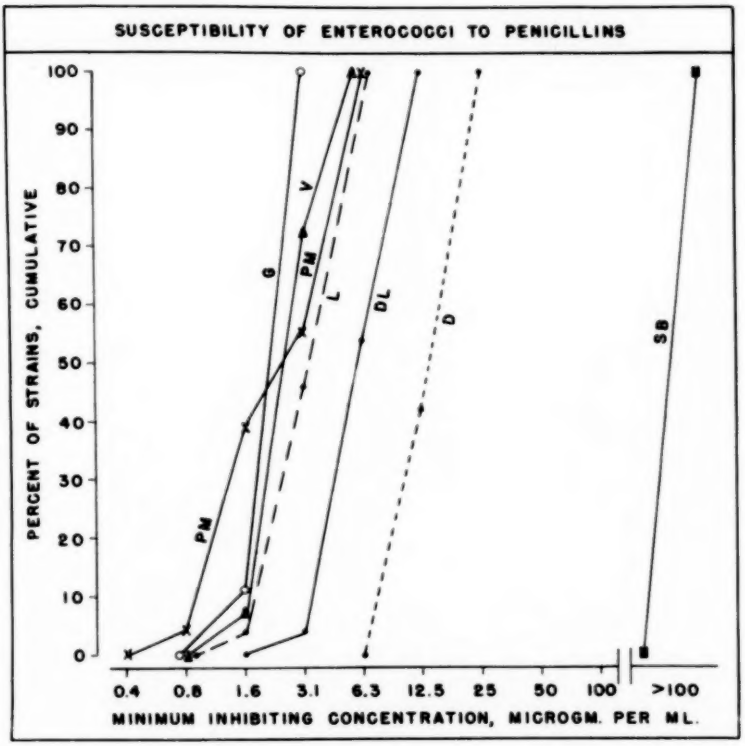

Fig. 5

Enterococci. These were all of serologic group D and were resistant to 6% sodium chloride and 56° C. but they were not classified further. These strains were remarkably uniform in their susceptibility to each of the penicillins, the greatest variation in activity being exhibited by PM which inhibited nearly all of the strains in concentra-

tions of 1.6 to 6.3 μg. per ml. None of the strains were inhibited by SB in the highest concentration used, namely 100 μg. per ml. The results are summarized in Table 3 and Fig. 5. For about 40% of the strains, PM was the most active; for the others the order of activity was: G ≥ V ≥ PM ≥ L > DL > D > SB.

bility of different strains of gonococci to each of the penicillins, but penicillin G was clearly the most active. The order of activity of the different penicillins, as seen from Fig. 7, which includes the results of all the tests done by the different methods, was: G > V = PM > D > DL > L > SB. All of the strains were

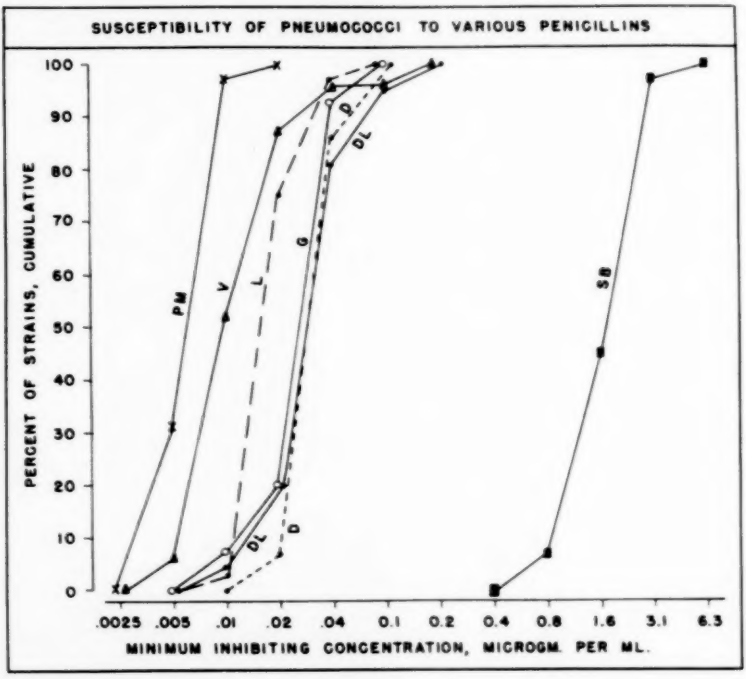

Fig. 6

Pneumococci. These strains were all bile soluble and type-specific. They too were fairly uniform in their susceptibility to each of the penicillins. Nearly all of them were inhibited by SB in concentrations of 0.8 to 3.1 μg. per ml. The order of activity of the penicillins against most of these strains as seen in Fig. 6, was: PM > V > L > G = DL = D > SB.

Neisseria gonorrhoeae. There were fairly wide variations in the susceptibility of different strains of gonococci to each of the penicillins, but penicillin G was clearly the most active. The order of activity of the different penicillins, as seen from Fig. 7, which includes the results of all the tests done by the different methods, was: G > V = PM > D > DL > L > SB. All of the strains were inhibited by SB in concentrations of 0.8 to 6.3 μg. per ml.

Neisseria meningitidis. Only 8 strains were tested. These were all much less sensitive than *N. gonorrhoeae* to all the penicillins, but they were much more sensitive to G than to any of the others. The order of activity of the penicillins, as seen in Table 3, was: G > PM > V ≥ SB ≥ D ≥ DL ≥ L.

It is interesting to note that for both

species of Neisseria the relative activity of the phenethicillin stereoisomers is the reverse of that seen for the Gram-positive cocci, the L-isomer being the most active against the latter and the D-isomer being the most active against the Neisseria. The DL mixture was generally intermediate in activity, more nearly approximating that of the L form, in keeping with its greater proportion of that form.

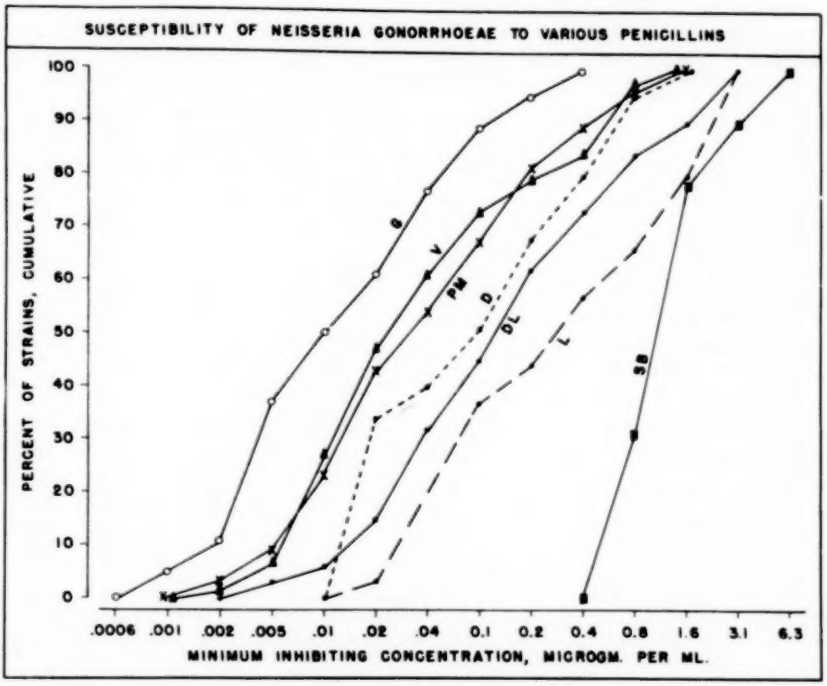

Fig. 7

Hemophilus influenzae. Some difficulties were encountered in the preliminary tests with these strains. In some of those tests, growth of all strains occurred in the highest concentrations of all the penicillins, namely 100 μg. per 100 ml. This may have been due to the luxurious growth of the seed cultures on the chocolate agar, the surface growth of which was harvested and suspended in broth to use for the inoculum on the antibiotic containing media. When this suspension was diluted to provide an inoculum of 10^{6-7} organisms on the solid medium and about 10^5 organisms per ml. in the liquid medium, the results of the tests with penicillin G corresponded more closely to those obtained in another recent study (Hirsch and Finland[14]). In the tests with these strains the results obtained by each of the 3 methods were very similar as seen from Table 3 and Fig. 8. The order of activity of the penicillins against most of the strains was: G > PM > V > L = DL > D > SB. More than 80% of the strains were inhibited by SB in concentrations of 6.3 to 100 μg. per ml.

Hemophilus sp. There were 8 atypical strains of Hemophilus that were

not fully classified as shown in Table 3. These strains were much less sensitive to G and PM, and relatively more susceptible to the other penicillins, particularly V, than were the strains of *H. influenzae*. All 8 strains grew uninhibited in 100 μg. per ml. of SB. The order of activity of the penicillins against these 8 strains was G = V > DL > D = L ≥ PM > SB; this is approximately the same order of activity as for *H. influenzae* except for the lower position of PM, but the difference between the activity of PM and that of the phenethicillins was slight.

Pasteurella multocida. The 6 strains of this species were moderately sensitive to G, but they were much more sensitive to V and PM. Most of them were apparently less sensitive to DL or L than to D. Tests with SB were not done with these strains. The order of activity of the other penicillins against these 6 strains was: PM ≥ V > G = D > DL = L.

Mima polymorpha. The 4 strains tested were moderately susceptible to G and equally or more so to PM. They were inhibited by SB in concentrations of 1.6 to 50 μg. per ml. The order of activity was: PM > G > V > DL ≥ D ≥ L > SB.

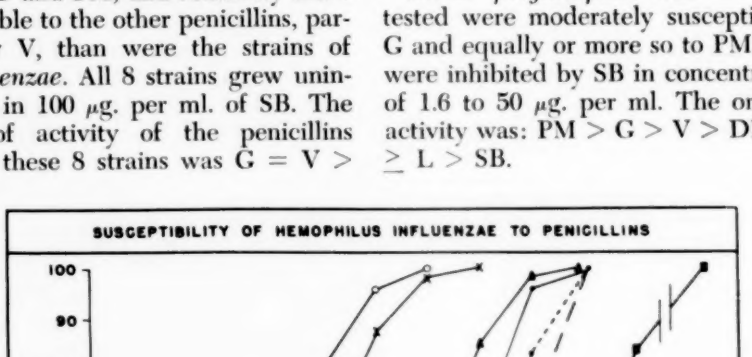

Fig. 8

Salmonella. The 7 strains included 1 S. *typhimurium* and 3, 2 and 1 classified as groups B, C and D, respectively. All were inhibited by 50 to 200 μg. per ml. of G and all but one of them were as susceptible or more so to SB. Most of the strains were slightly less susceptible to PM and V than to G. None were inhibited by 400 μg. per ml. of any of the phenethicillins. For most of these strains, therefore, the order of activity of the penicillins was: SB > G > V = PM > D = L = DL.

Shigella. Of the 16 strains, 9 were

S. *sonnei* and the others were not classified. All required 100 or 200 μg. of G and 200 to 400 μg. of the other penicillins to produce infection, except for the phenethicillins; all the strains grew uninhibited in 400 μg. per ml. of the latter except one strain which was sensitive to 100 μg. per ml. of each of them.

Escherichia coli. The 19 strains tested represented 4 specific serotypes. They were inhibited by 200 or 400 μg. per ml. of G, V, PM and SB, but not by the largest concentration of any of the phenethicillins used, namely 400 μg. per ml. Only 4 strains were more susceptible to SB than to G, the rest were equally susceptible or less so.

Other Gram-Negative Bacilli. Only occasional strains of *Klebsiella pneumoniae* and Proteus were inhibited by high concentrations of some of the penicillins; the rest of the strains of these organisms as well as those of Aerobacter, Herellia and Pseudomonas grew uninhibited in 400 μg. per ml. of all the penicillins.

COMPARISON OF ACTIVITY OF DL-PHENETHICILLIN AND PENICILLIN V. From the last column in Table 3 and from Fig. 2 it can be seen that DL was considerably more active than V against penicillinase producing staphylococci. On the other hand, the data in that table and in Figs. 1 and 3 to 8 show that the nonpenicillinase producers and strains of nearly all other species tested were generally more susceptible to V than to DL. When the relative activity of individual strains was compared in simultaneous tests, 61% of strains of penicillinase producing staphylococci were more susceptible to DL than to V and the remaining 39% were equally sensitive to both (considering strains not inhibited by the maximum concentration used as being equally susceptible). Of all the other strains of the different organisms similarly tested, 70% were more susceptible to V than to DL, 18% were equally sensitive to both and only 12% were more sensitive to DL. The differences ranged up to 32-fold, but for the great majority of strains they were only 2- or 4-fold.

COMPARISON OF THE PHENETHICILLIN ISOMERS. Minor quantitative differences in the susceptibility of individual strains to the isomers of phenethicillin are difficult to interpret. The general order of activity of these isomers appears to be similar for nearly all strains of the species, but according to the present findings, this varied considerably for different species. The activity of DL, which contained about two-thirds L and one-third D, corresponded to that which was to be expected if each of its constituents acted independently.

In nearly all tests with Gram-positive organisms, L was the most active, D the least active and the activity of DL was intermediate. Moreover, as the difference in activity of D and L increased, the difference between DL and L decreased, as was to be expected, so that their activity often appeared to be the same within the limits of error of the method. These relationships appeared to be different for the Gram-negative bacteria. Against Neisseria and Pasteurella, D appeared to be the most active, L the least active and the activity of DL was intermediate or the same as that of L. The tests with the strains of Hemophilus and Mima were somewhat irregular in this respect; all 3 isomers appeared to be more or less equal in activity against many of them, but D was less active than L and DL against most of the strains of *H. influenzae*. Against Herellia and nearly all of the enteric Gram-negative bacillary organisms none of the phenethicillins exerted any inhibitory action in the highest concentrations used, namely 400 μg. per ml.

ACTIVITY OF SYNNEMATIN B. Some of the interest in synthetic penicillins is based upon earlier observations which indicated that cephalosporin N, or synnematin B, was more active than penicillin G against Salmonellas although less active against Gram-positive organisms. SB is a penicillin which has a 4 amino, 4 carboxy-,n-butyl group attached to 6 APA instead of the benzyl group of G or other cyclic side chains of V, PM or phenethicillins. As seen from Table 3 and Figs. 1 to 8, the activity of SB in the present study was slightly greater than that of G against some of the strains of Salmonella, approached that of G against strains of Shigella and *E. coli*, but it was much less active against all other species, especially those of Gram-positive cocci. The variable relationships of activity of G and SB were also reported recently by Berryman and Sylvester[4].

RESULTS OF TESTS WITH 6-AMINOPENICILLANIC ACID. Early in these studies, aqueous solutions of pure 6APA were provided by Lilly Laboratories in sterile vials containing 250 mg. per ml. These were kept in a refrigerator at 4° C. The results of the tests with this material, which were carried out with nearly all of the strains, have not been included with the others because it was subsequently learned that such solutions were not very stable under these circumstances. Later, 6APA was supplied as a dry sterile powder in sealed vials, but many of the tests had already been completed when these were received. Both the solutions and powder showed varying activity against different species that can be summarized briefly. Nearly all of the Gram-positive cocci listed in Table 1 except the staphylococci were tested; they were all inhibited by 50 to 200 μg. per ml. of the solution and most of them were inhibited by 25 to 50 μg. per ml. of the freshly constituted material. Enterococci, however, were not inhibited by 200 μg. per ml. Gonococci were susceptible to 3.1 to 100 μg. per ml. and most of them were inhibited by 6.3 μg. per ml. of the freshly prepared material. Strains of meningococci and *Mima polymorpha* were inhibited by 25 μg. per ml., but strains of all other Gram-negative organisms, including those of Hemophilus and Pasteurella, were not inhibited by the largest concentrations used, generally 200 or 400 μg. per ml.

Discussion. Some of the early reports on differences in activity of the "natural penicillins" isolated during fermentations, namely G, F (Δ^2-pentenyl), dihydro F, K (n-heptyl) and X (p-hydroxybenzyl), were reviewed by Jennings[16]. The possible clinical significance of such differences was realized only after a study of the causes of the declining activity of commercial penicillins in the treatment of syphilis[5,6]; this was shown to be due to the presence of increasing amounts of penicillin K, which proved to be relatively unstable and hence of considerably reduced activity in the body.

In the present study as in those reported by others (Garrod[8], Gourevitch, Hunt and Lein[10]) marked differences in activity of different penicillins were revealed and these varied for different species of organisms. Of particular interest was the striking difference between the activity of D- and L-isomers of phenoxyethyl penicillin, the former being much less active than the latter groups B, C, G and D streptococci and more active against Neisseria (see Table 3).

The data presented thus indicate the importance of surveying the activity of new penicillins whenever feasible against many strains of the varieties of bacterial pathogens against which they may be used therapeutically, in addition to comparing their absorption, excretion and toxicity, before their potential therapeutic value can be com-

pared with that of products already available. The present data indicate that by comparison with penicillins V and G, phenethicillin, as currently available for therapy, is actually less active weight for weight, and hence any advantage of its better absorption from oral administration is lost, particularly as compared with penicillin V, which is also well absorbed (McCarthy and Finland[18]). Only against penicillinase producing staphylococci was phenethicillin found to be more active than G or V, but other studies have shown that this advantage is reduced progressively as the concentration of the staphylococci is increased (Geronimus[9], Wallmark and Finland[23]). Since the numbers of staphylococci in infected lesions are even greater than those in fully grown cultures, no advantage may be expected in the effects on the infected lesions (Geronimus[9] and Wallmark and Finland[23]). Although it is possible that the small numbers of organisms that might escape into the circulation from the lesion would be affected, it is also true that small numbers of penicillinase producing organisms are more susceptible than large ones to the action of penicillins V and G (Wallmark and Finland[23]).

Although the 6APA used was not specifically tested in this laboratory for the presence of other penicillins, it seems unlikely that the small amount of activity that was demonstrated was actually due to small amounts of penicillin as impurities.

Summary and Conclusions. *In vitro* tests for the susceptibility of 552 strains of 20 species or genera of bacteria were carried out with the following: benzyl penicillin (G), phenoxymethyl penicillin (V), DL-phenoxyethyl penicillin (phenethicillin) and its individual D and L isomers, phenylmercaptomethyl penicillin (PM), synnematin B (SB) and the common nucleus of all of them, 6-aminopenicillanic acid (6APA). The different penicillins varied markedly in their action against the different species and genera, and to a varying extent against strains of the same species. Phenethicillin was more active than V or G against the majority of strains of penicillinase-producing *Staphylococcus aureus*, but the great majority of strains of all other organisms were more susceptible to V and especially to G. The activity of PM closely approximated that of G against most organisms, but the former was more active against many of them. SB was slightly more active against some strains of Salmonella and about as active against Shigella and *E. coli* as penicillin G, but it was much less active against all other species, particularly those of Gram-positive cocci. Some activity was also exhibited by 6 APA against many of the organisms tested.

The importance of considering the antibacterial activity of new penicillins as well as their absorption and other properties, when comparing their therapeutic potentials with those of currently available ones, is thus emphasized.

ADDENDUM. After completion of this study, a supply of 2,6 dimethoxyphenyl penicillin (DMP) was made available by Bristol Laboratories. This new penicillin is of great interest because it is only very slowly and minimally affected by staphylococcal penicillinase. A number of reports of laboratory and clinical studies made with this penicillin have already appeared in the British Medical Journal for September 3 and in the Lancet for September 10, and others were presented at a conference in Syracuse, N.Y. on September 7, 1960, and will be published in a monograph. Because of the considerable interest in this new penicillin and its potential importance, its *in vitro* activity against a number of strains of common bacterial pathogens was studied by the replica-inoculating method of Steers *et al.*[22] (except for the strains of Proteus which were tested by the broth dilution method) with the assistance of Dr. Bosko Postic. The results are summarized in Table 4.

TABLE 4.—COMPARISON OF ACTIVITY OF PENICILLIN G AND DIMETHOXYPHENYL PENICILLIN (DMP) AGAINST 234 STRAINS OF BACTERIAL PATHOGENS

Organism*	No. of Strains	M.I.C. of G, μg./ml.		M.I.C. of DMP, μg./ml.		Ave. Ratio: DMP/G
		Range	Median	Range	Median	
Staphylococcus aureus R	36	50–>200	>200	3.1–6.3	3.1	<0.02‡
" " S	20	0.1–0.4	0.2	3.1	3.1	15‡
Streptococcus pyogenes, group A	30	0.0025–0.1	0.005	0.2–0.4	0.4	20
" " , groups B & C	15	0.01–0.1	0.02	0.2–3.1	0.4	13
" " , group G	12	0.005–0.04	0.01	0.4–12.5	0.4	50
Streptococcus viridans	19	0.1–1.6	0.8	0.2–6.3	3.1	4
Enterococcus (group D)	27	1.6–3.1	3.1	≥100	>100	>50
Diplococcus pneumoniae	14	0.01–0.02	0.02	0.1–0.4	0.2	10
Neisseria gonorrhoeae	2	0.02–0.2		0.8		
Hemophilus influenzae	10	0.8–3.1	1.6	6.3–25	25	18
Proteus mirabilis	20	6.3–100	12.5	>100	>100	>16
" *vulgaris*	2	>100		>100		
Escherichia coli	17	>100		>100		
Klebsiella pneumoniae	10	>100		>100		

*R = resistant, penicillinase producer; S = sensitive, nonpenicillinase producer.
†With a small inoculum (100 or 1000 organisms) the average ratio of DMP/G was 6.
‡With an inoculum of 10^4 organisms or less, M.I.C. of G was 0.02 to 0.04, that of DMP was 1.6 to 3.1, and the average ratio DMP/G was 80.

It is seen that DMP was quite uniformly active against all strains of staphylococci and essentially equally so against producers and nonproducers of penicillinase. It is thus very much more active against the former and much less active against the latter. The superiority of DMP over other penicillins, based on this study and on the other reports, is thus limited to its activity against penicillinase-producing staphylococci. This, however, may be a crucial factor in the treatment of infections with such organisms.

DMP, which has been given the trade name Staphcillin by Bristol Laboratories in this country, and Celbenin by Beecham Research Laboratories in England, is essentially unabsorbable after oral administration and must, therefore, be given in large doses parenterally.

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SUMMARIO IN INTERLINGUA

Activitate in Vitro de Varie Penicillinas

Esseva executate in vitro tests del susceptibilitate de 552 racias de 20 species o generes de bacterios pro le activitate de penicillina benzylic (G), de penicillina phenoxymethylic (V), de penicillina DL-phenoxyethylic (penethicillina) e su dextero- e levo-isomeros individual, de penicillina phenylmercaptomethylic (PM), de synnematina B (SB), e del nucleo commun de illos omnes, acido 6-amino-penicillanic (6APA). Le varie penicillinas variava marcatemente in lor activitate contra le varie species e generes e a variabile grados contra le varie racias del mesme specie. Phenethicillina esseva plus active que penicillina V o penicillina G contra le majoritate del racias de *Staphylococcus aureus* (que es un productor de penicillinase), sed le grande majoritate del racias de omne le altere organismos esseva plus susceptibile pro le activitate de penicillina V e plus ancora de penicillina G. Le activitate de penicillina PM esseva proximissime a illo de penicillina G con le majoritate del organismos, sed il remaneva un notabile numero de racias contra le quales penicillina PM esseva plus active. SB esseva levemente plus active contra certe racias de Salmonella que penicillina G. Le duo agentes habeva plus o minus le mesme activitate contra Shigella e *Escherichia coli.* Sed SB esseva multo minus active que penicillina G contra omne le altere species, particularmente le species de coccos positive al Gram. Un certe grado de activitate esseva etiam manifestate per 6APA contra multes del organismos testate.

Le datos sublinea le importantia de considerar le activitate antibacterial del nove penicillinas si ben como lor absorption e altere proprietates quando lor potentiales therapeutic es sub comparation con illos del currentemente disponibile penicillinas.

INCISION AND SUCTION FOLLOWING INJECTION OF RATTLESNAKE VENOM*

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The problem of deciding which data derived from experiments on small animals can be applied to man is one for which there is no easy solution. While data enjoy their highest degree of applicability with the specific kind of animal involved in the experiment, they must sometimes be applied to other animals, including man. There is no established criterion for the transfer of information based on experiments in one kind of animal to another kind of animal. When data obtained on the mouse must be applied to information on the human, the investigator should exercise extreme caution, and must be ready to admit in those cases where the data prove to be unreliable, that the mouse is a very poor human being.

In dealing with complex mixtures of enzymes, non-enzymatic proteins and non-proteins such as occur in some animal venoms, it has become increasingly apparent that not all data obtained on experiments in lower animals can be applied to man. In some instances, information obtained on small mammals has been accepted for application in humans in spite of adequate clinical experience to indicate that the information is inapplicable. The wise investigator, or clinician, is one who knows the limitations for the application of these data; he might, for instance conclude that incision and suction are indicated in treating snakebites in rodents, and yet not wish to imply that this is the same conclusion that can be reached for man.

The responsibility for interpreting and applying experimental data must rest first with the experimenter. Unfortunately, interpretation is often rendered by far less competent individuals who, without benefit of the actual research experience, feel inclined both to interpret the data and determine their application. The investigator should, whenever possible, consider where and how his information can be best fitted into the over-all problem. Obviously, an investigator confronted with evidence that incision and suction are effective against rattlesnake bites in rodents will consider the possibility that his data may be applied to man. Obviously also, he is responsible for interpreting and applying his data with all the caution that prudence and experience can suggest.

Few problems in venomology, or the treatment of ophidiasis, have elicited as much controversy as the measures of incision and suction. A critical review of this problem has recently been

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published by Parrish[8]. A careful examination of the papers described in Parrish's report indicates that a share of the disagreement concerning incision and suction can be ascribed to differences in the experimental methods and the choice of venom and test animals used in the experiments.

Incision and suction have been used by the senior author in the treatment of snake venom poisonings in those cases where such measures could be instituted within the first hour following envenomization[9,10]. Longitudinal incisions of one-quarter inch in length through the fang marks have been advised in those cases where the offending rattlesnake has been a large one, or the victim a child. The direction of the animal's strike and the curvature of the fang should be borne in mind when determining the plane of the incision. The depth of fang penetration is taken as approximately three-quarters of the distance between the two fang marks. In those cases where only one fang has entered the tissues, and the offending snake has not been caught, an incision to a depth of one-quarter inch has been made. The author's experiences with this technique of incision and suction have been very encouraging. Multiple incisions over the involved extremity or in advance of progressive edema are not advised. A limited number of experiments in dogs and rabbits, similar to those described by Jackson and Harrison[5], indicated that a substantial amount of hemorrhagic exudate could be removed from an incised wound over an area in which venom had previously been injected. The exudate, when injected intravenously into a second animal caused the same deleterious changes as freshly prepared venom. In view of these clinical and experimental experiences the authors have advised incision and suction for certain rattlesnake bites in human beings.

In 1957 Leopold, Huber and Kathan[7] demonstrated that rabbits receiving 4 to 6 mg. of *Crotalus adamanteus* venom per kg. of body weight, a) immobilized and subjected to immediate incision and suction, had a shorter survival period than those rabbits injected with an equal amount of venom and immobilized without subsequent incision and suction; b) immobilized rabbits having a tourniquet above the area of the injected venom survived longer than those receiving immobilization and incision and suction; and c) immobilized rabbits survived as long as those immobilized and treated with a tourniquet above the area of the venom. In spite of the statement by the authors that their experiments did not follow the standard method of tourniquet, incision and suction, reports have appeared which indicate that questionable applications of these data have been made.

In the studies by Leopold, Huber and Kathan[7], suction over the area of envenomation was maintained for only 15 minutes. The present authors are of the impression, following considerable correspondence, that there are very few, if any, physicians treating rattlesnake bites in *Homo sapiens* who advise, or feel, that suction limited to 15 minutes' duration is effective. Also, most clinicians combine incision and suction with the use of the tourniquet; this combination was not evaluated in the experiment. Leopold, Huber and Kathan[7] determined the effectiveness of their various treatments on the basis of the length of the interval between institution of therapy and time of death. In Jackson and Harrison's[5] study evaluation was made on the basis of the number of animals that survived or died. During previous studies on venoms we have found that the relationship between the time of institution of a therapeutic measure following envenomization, and death-time is a

reliable criterion for determining effectiveness, but only under very specific conditions. These conditions have been discussed by Burn, Finney and Goodwin[1], Finney[4], and Christensen and Finney[3]. We have found that certain venoms can be assayed intravenously using the death-time as a response metameter providing that the logarithm of the dose is used as the dose metameter and the logarithm of the death-time as the response metameter, and providing that the doses fall within the range over which the two metameters are linearly related. This finding is in agreement with that of Christensen[2]. An analysis of the data submitted by Leopold, Huber and Kathan[7] indicates that certain of their conclusions may not be valid.

More recently Leopold and Huber[6] reported that when 40 mg. of *Crotalus adamanteus* venom was introduced into a previously made wound on the thigh of a rabbit, subsequent incision and suction for 30 minutes not only failed to prolong the survival time of the animal, as compared with a control, but actually shortened it. The report states that the 40 mg. dose per rabbit was chosen because this "was arbitrarily considered to be the minimum that must be removed from a wound in a human." It hardly seems reasonable to subject a rabbit to such a large dose of venom and expect it to survive, regardless of the first aid measure used. Even if 80% of the venom had been removed by incision and suction the animal would still have received a lethal dose of venom. The authors note that "all the animals died suggesting that suction is not an effective method of removing venom from an open wound." One must certainly be dubious of the rationale that since 40 mg. "is the minimum amount that must be removed from a wound in a human," that amount must also be removed from a rabbit. The critical question is, how much venom was removed during suction in these animals?

In 1957, at this laboratory, a study was initiated to determine by chemical and zootoxicological methods, the effectiveness of incision and suction for removing venom injected into rabbits. The present report deals with the changes elicited in the rabbits cardiovascular system following intravenous injection of the supernatant of the hemorrhagic exudate removed during suction from a wound in an envenomized rabbit.

Materials and Methods. Fifty-four rabbits weighing between 3.2 and 4.6 kg. were studied during the investigation. Fourteen of these animals were used in determining the MLD. The venom of *Crotalus adamanteus* was used in 15 experiments and *Crotalus atrox* in 5. The intramuscular MLD's for *C. adamanteus* and *C. atrox* venoms were established at 1.0 mg. per kg. and 1.9 mg. per kg. of body weight respectively. The venom was prepared in physiological saline so that 0.2 ml. contained 3 MLD.

The first test rabbit of each series in the first group of experiments was immobilized in the prone position, an area over both biceps femoris muscles shaved, and the venom injected in the left muscle mass through a 20-gauge needle to a depth of 0.5 cm. Within 2 minutes a cruciate incision of 1.5 cm. in length and 0.5 cm. in depth was made through the site of the injection and suction applied by means of a Cutter rubber suction cup. The hemorrhagic exudate was removed from the cup at 5-minute intervals over a period of one hour in 7 rabbits, and over a period of 2 hours in 5 other rabbits. In the 5 rabbits the exudate was divided into a first- and second-hour sample. On the contralateral limb, 0.2 ml. of saline was injected, the area incised and suction applied for the same period of time. The exudate from this latter wound was used as the control sample. The hemorrhagic exudates were centrifuged at 2,000 r.p.m. for 20 minutes and the supernatants removed.

The second test rabbit of each series in group one was anesthetized with pentobarbital sodium (40 mg. per kg.) and prepared for the measurements of systemic arterial and venous pressures. Following equilibration the rabbit was given the control sample

intravenously. Five minutes later the second-hour sample from the envenomized limb in the group of 5 rabbits was injected, followed at 5 minutes by the first-hour sample. In the remaining 7 rabbits the single one-hour sample was given. All injections were adjusted to the same volume with physiological saline. The time of death of the animal was recorded.

to a Medcraft model D, 8-channel electroencephalograph. Respirations were recorded by means of a cantilever pneumograph fed into the electroencephalograph. Cisternal pressure was measured through a 20-gauge needle fixed in the cisterna cerebellomedullaris, and connected to a modified Brodie tambour in parallel with a water manometer. The tambour activated a wire strain-gauge

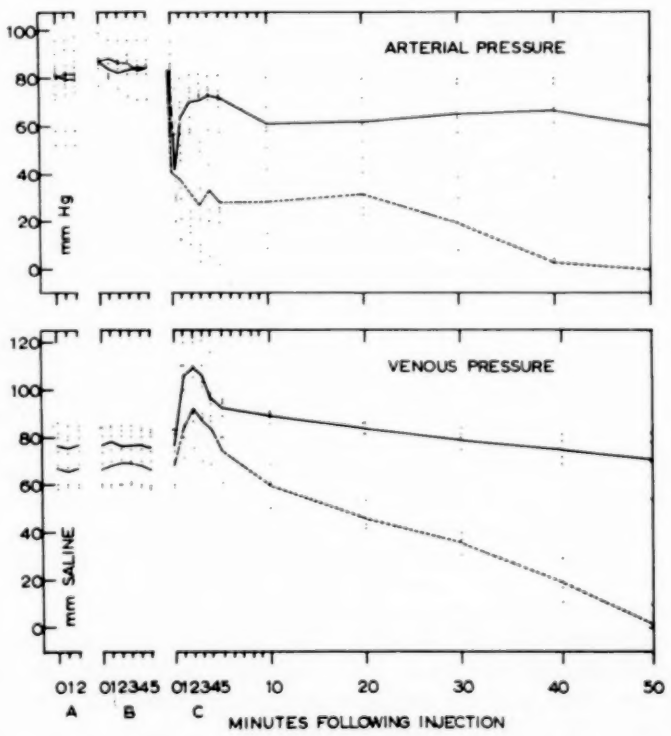

Fig. 1.—Changes in systemic arterial and venous pressures following intravenous injection of: *A*, control sample; *B*, second-hour sample; *C*, first-hour sample. Dotted line denotes mean blood pressures for non-surviving animals.

In a second group of 8 experiments the exudates were collected over a period of one hour in the same manner, and were then injected into rabbits prepared as follows:

Under pentobarbital anesthesia a common carotid artery and femoral vein were cannulated for the measurement of arterial and venous pressures. Bipolar electrodes were placed in the skull over the frontal, parietal and occipital lobes, bilaterally. Conventional limb, unipolar extremity, and precordial leads were affixed. All electrodes were connected transducer which modulated the amplitude of a 3-cycle carrier feeding the response into the electroencephalograph. A femoral vein was cannulated for the injection of venom; all animals were heparinized.

Results. Figure 1 shows the changes produced by the various exudates in the systemic arterial and venous pressures in the first group of experiments. The control sample provoked no

change in either parameter; the second-hour sample from the envenomized limb produced only minor changes in both pressures; these changes were variable and transient. Following injection of the first-hour sample there was an immediate fall in systemic arterial pressure concomitant with an increase in venous pressure. In 4 animals death occurred within 12 minutes; 3 others died within 45 minutes and the remaining 5 animals died between 2 and 24 hours. At necropsy those animals surviving more than 5 hours showed pulmonary and visceral congestion; retroperitoneal or intraperitoneal hemorrhage, or both; hemorrhages into the lumen of the bowel; hemorrhages in the mediastinum or heart, or both; and hemorrhages into the muscles of the extremity in which the exudate had been injected.

Of the 12 first test rabbits in group one, 5 died between 10 and 24 hours; 5 died between 24 and 48 hours; one died at approximately 50 hours and one was alive one week later. The findings at necropsy were similar to those observed in the second test animals.

The average volume of the supernatant of the hemorrhagic exudate from the envenomized limb was 2.6 ml. for the first hour and 2.3 ml. for the second hour. The pH ranged from 7.0 to 7.6. On the control limb the average volume was 2.0 ml. for the first hour and 1.0 ml. for the second hour. The pH ranged from 6.9 to 7.3.

In the second group of 8 experiments, the control samples provoked no change in the systemic arterial, venous or cisternal pressures, respiratory rate, or the electrocardiogram or electroencephalogram. The second-hour sample from the envenomized limb produced, in most rabbits, only minor changes in arterial pressure, cardiac rate and respiration. These changes were transient. Injection of the first-hour sample produced an immediate fall in systemic arterial pressure concomitant with a rise in venous and cisternal pressures similar to those seen in the first group of experiments.

The changes in the electrocardiograms were subject to some variation. In those animals displaying more minimal degrees of shock there were only minor changes in rate and rhythm. Animals showing slightly greater degrees of shock had ST segment and T wave changes indicative of mild ischemia. Those rabbits in which shock was most profound displayed tachycardia with marked ST segment and T wave changes followed by ventricular arrhythmias and sometimes complete heart block.

The depression in central nervous system electrical activity was associated with the fall in systemic arterial pressure. In general, the exudate caused depression in the amplitude of the normal wave pattern and in spindle burst activity. There was no convulsive activity.

The respiratory changes were subject to some variation. In those animals which died within 2 hours, respiratory rate was usually decreased immediately following injection of the exudate. In some cases there was apnea of varying durations. Most respiratory movements following injection of the exudate tended to be more superficial and abdominal in type. In several animals respirations ceased during the initial fall in systemic arterial pressure and might not have resumed except for the intermittent artificial respiration which was carried out. Artificial respiration did not appear to alter the over-all effects of the cardiovascular collapse.

Discussion. The experiments indicate that suction over an incised area where *C. adamanteus* or *C. atrox* venom has been injected removes an exudate

which exhibits many of the known zootoxicologic properties of *Crotalus* venom. While it is possible that this exudate may contain certain active autopharmacologic substances stimulated in the animal following envenomization, or in response to a combination of the venom and incision and suction, it appears that the over-all reaction to the exudate is strikingly similar to that observed following injection of crude *Crotalus* venom (Russell, Michaelis and Engelbert[12], Russell, Emery and Long[11], Russell and Michaelis[13], Witham, Remington and Lombard[14]). It is difficult to compare the amount of the deleterious material removed by suction with the amount of venom initially injected into the animal. However, when the material was tested in mice to determine its LD_{50} it appeared to have a high degree of toxicity. Also, preliminary chemical studies indicate that the exudate has properties not unlike those of the venom. The evidence thus indicates that the material removed during suction is similar in its zootoxicological, chemical and lethal properties to that of crude *Crotalus* venom.

If exudate removed during suction contains venom then its removal should increase the animal's chances for survival. If, on the other hand, the mechanism of incision and suction when applied to rabbits stimulates a deleterious reaction which enhances the action of the venom, then it is possible that incision and suction might lessen the animal's chances for survival. While there is no evidence to date to suggest that incision and suction in themselves produce changes which would enhance the activity of venom *in vivo*, there is the possibility that, in the rabbit, incision to the extent used by Leopold, Huber and Kathan[7], as well as by ourselves, without the benefit of anesthesia, might induce in addition to pain other responses deleterious to the animal. These responses might include local tissue reactions, neural, muscular and glandular activity and the establishment of a state of hyperexcitability within the central nervous system at the segmental and suprasegmental levels. These reactions, particularly the hyperexcitability, might possibly enhance the lethal property of the venom and thus alter the MLD or LD_{50}. Under such circumstances it might be reasonable to infer that incision and suction in the rabbit can decrease tolerance to the venom. However, it does not follow that a similar trivial operation performed upon human beings following rattlesnake envenomization (Russell[9]) would be an important factor in contributing to the over-all reaction of this much larger and different organism. Within a proper frame of reference the findings by Leopold, Huber and Kathan[7], and Leopold and Huber[8] are consistent but if their data are to be applied to an evaluation of the usefulness of incision and suction in man then the adequacy of their techniques must be questioned.

Summary. A study was made of certain zootoxicologic effects of a hemorrhagic exudate removed by suction from the limb of a rabbit which had been inoculated with *Crotalus* venom. The supernatant of the exudate, when injected intravenously into another rabbit, produced a fall in systemic arterial blood pressure, an increase in systemic venous and cisternal pressures, changes in the cardiac and respiratory rates, and alterations in the electrocardiogram and electroencephalogram. These changes were similar to those that have been observed following the intravenous injection into animals of crude *Crotalus* venom.

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SUMMARIO IN INTERLINGUA

Incision e Suction post Injection de Veneno de Crotalo

Esseva executate un studio de certe effectos zootoxicologic de un exsudato hemorrhagic obtenite per suction ab le extremitates de un conilio que habeva recipite un inoculation de veneno de crotalo. Le supernatante del exsudato, quando injicite per via intravenose in un altere conilio, produceva un reduction del tension de sanguine arterial in le circulation major, un augmento del tension de sanguine venose in le circulation major e del tension de sanguine cisternal, alterationes in le frequentias cardiac e respiratori, e alterationes del electrocardiogramma e del electroencephalogramma. Iste alterationes esseva simile a illos que ha essite observate post le injection intravenose in animales de veneno de crotalo in forma crude.

SERUM CHOLESTEROL IN NORMAL MALES VERSUS MALES WITH CORONARY HEART DISEASE: DIFFERENCES WITH RESPECT TO AGE*

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Of the several measurements used in the evaluation of serum lipids, the total cholesterol determination is probably most widely accepted and utilized as a practical and useful indicator of lipid changes that may reflect predisposition to coronary heart disease (Clough[1]). However, the great variability in the serum cholesterol levels, as noted both in normal persons and in patients, has led some to conclude that this measurement is of little or no value as a predictor of atherosclerotic heart disease. That data have been published which may modify this latter view, when the age of the subject is taken into consideration (Lawry *et al.*[5], Mattingly *et al.*[6]), is perhaps not widely appreciated.

It is the purpose of this report to present a retrospective study in which the serum cholesterol levels in male subjects, with and without clinical evidence of coronary heart disease, have been evaluated in relation to age. Our results are consistent with the findings of others, and support as statistically valid the suggestion that serum cholesterol determinations may prove useful as an index of coronary disease in younger subjects.

Material and Method. In this study data were obtained from 95 male subjects without known cardiovascular disease for the control "normal" group (age range 30 to 59), and from 88 male patients with confirmed myocardial infarction or with typical angina pectoris for the coronary heart disease group (age range 33 to 59). The control subjects included medical students, hospital employees and members of a prepaid medical plan.† Each had undergone a recent history and physical examination, screening laboratory work (serology, blood count and urinalysis) and a roentgenogram of the heart. Most of the patients were studied on an

*This study was supported in part by a grant-in-aid from the Washington Heart Association, Washington, D.C.

†We are indebted to physicians of the Group Health Association, Washington, D.C., for permitting the sampling of its members undergoing annual medical examination.

outpatient basis. In-patients with recent myocardial infarcts were sampled as long after the acute episode as was practicable to minimize the effects of stress and none was receiving heparin therapy.

Serum cholesterol was determined by the method of Sperry and Webb[7]. The standard deviation for replicate determinations in this laboratory, obtained by analysis of specimens unknown to the technician, is 6.6 mg. per 100 ml. of serum. To simplify presentation of the data, the mean cholesterol values are reported according to age by decades. The linear regressions of cholesterol on age were computed for the control and test groups from the individual data.

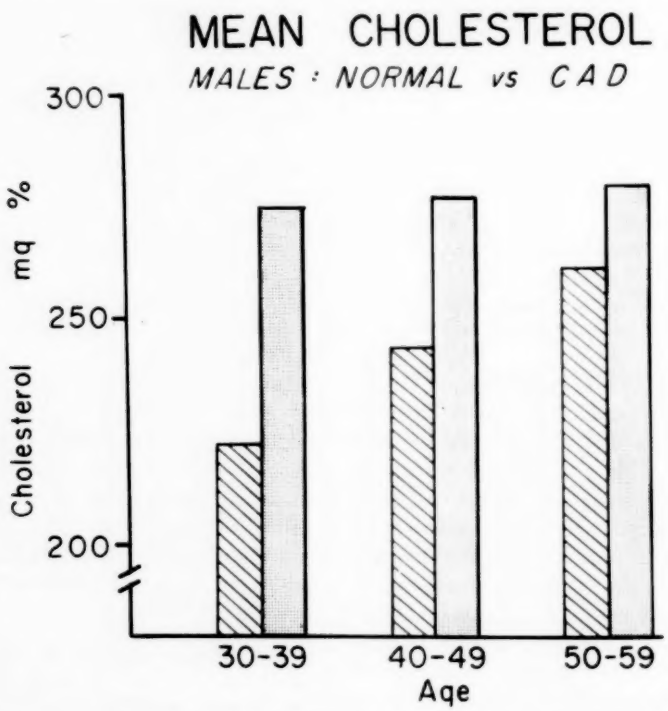

Fig. 1.—Mean serum cholesterol values of control "normal" subjects (cross-hatched bars) and patients with coronary artery disease (shaded bars) according to age by decades.

Results. The mean serum cholesterol of the subjects, according to age by decades, is shown in Fig. 1. The values for the control subjects increased with each decade and were 222 (range 145 to 295), 242 (range 154 to 360), and 259 (range 180 to 341) mg. per 100 ml. for the 4th, 5th and 6th decades, respectively. On the other hand, mean values for the coronary artery disease patients revealed little change with increasing age and were 271 (range 108 to 354), 280 (range 183 to 396), and 280 (range 178 to 439) mg. per 100 ml. for the corresponding decades, respectively. Inspection of Fig. 1 shows that the greatest difference in the mean cholesterols of the control and the patient groups occurs at the 30 to 39 age range.

Further analysis of the data from the control males reveals that a statistically valid positive regression of cholesterol by age exists ($p<.01$). The

slope of the regression line indicates an average increase of 1.6 mg. per 100 ml. of serum cholesterol for each year of increase in age. In contrast, there is no significant regression of serum cholesterol by age in the coronary group. In other words, a plot of the cholesterols from this group falls about 3 arbitrary levels of cholesterol; namely, 250, 275, and 300 mg. per 100 ml. It should be apparent that these percentages give some indication of the capability of the cholesterol determination to discriminate between the control subjects and the patients. In an ideal experiment, if a test were completely

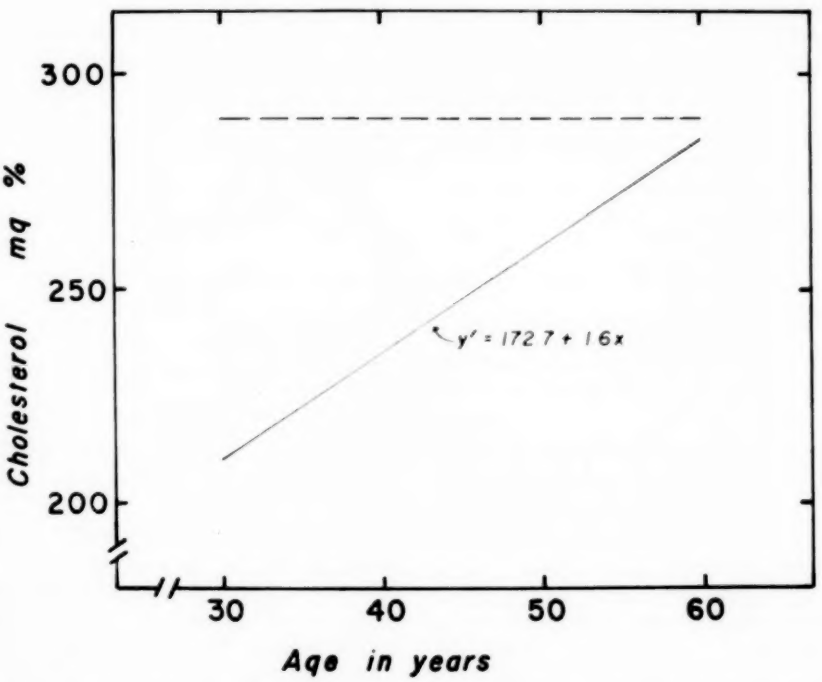

Fig. 2.—Regression line computed from individual cholesterol values for the control subjects (solid line). Horizontal (dotted) line represents the mean cholesterol level, 276.7 mg. per 100 ml. of serum, for the coronary subjects.

a horizontal line representing their average value of 276.7. The relationship of these two lines may be seen in Fig. 2. Again it is evident that, on the average, the greatest difference in serum cholesterol lies in the younger age group.

In Table 1 the data represent the percentage of the control subjects and patients in each decade that fall above specific and sensitive, the percentages in the control column would approach zero, whereas those in the coronary disease column would approach 100. Inspection of Table 1, using this criterion, reveals that the smallest overlap of the two groups lies in the 30- to 39-year range and that the maximum separation of the two groups would be at a cholesterol level of approxi-

mately 275 mg. per 100 ml.* For each of the 3 levels of serum cholesterol given, the differences in the percentages between the control subjects and patients lessens with increasing age. This reflects the greater overlap of cholesterol values between patients and controls with advancing age.

heart disease in the individual. Unfortunately, this study excluded subjects below the age of 40. Our data and those of Lawry and associates[5], summarized in Table 2, clearly indicate that a greater discrimination between controls and patients is achieved in individuals under the age of 40. A simi-

TABLE 1.—COMPARISON BY AGE OF THE PERCENTAGE OF SUBJECTS WITH AND WITHOUT CORONARY HEART DISEASE MANIFESTING SERUM CHOLESTEROL VALUES ABOVE 250, 275 AND 300 MG. PER 100 ML. OF SERUM

	Age 30–39		*Age 40–49*		*Age 50–59*	
	Control	*C.H.D.*	*Control*	*C.H.D.*	*Control*	*C.H.D.*
Number of subjects	29	13	33	26	21	28
Serum cholesterol above 250 mg./100 ml.	21%	69%	58%	69%	62%	79%
Serum cholesterol above 275 mg./100 ml.	14%	62%	33%	58%	32%	43%
Serum cholesterol above 300 mg./100 ml.	0	23%	23%	13%	14%	30%

Note: Percentages are expressed as the nearest whole percent.
Abbreviation: C.H.D. is coronary heart disease.

Discussion. Measurement of the serum cholesterol concentration is frequently included in the routine evaluation of patients over the age of 40 or 45. This practice is evidently due to the increased incidence of coronary heart disease in the fifth decade and the recognition that groups of patients with coronary disease have higher serum cholesterol than normal or control subjects (Davis, Stern and Lesnick[2], Gertler, Garn and Lerman[4]). In this regard it has been shown in a large sample of American men, aged 40 to 59, that clinical coronary disease was associated with an antecedent elevation of serum cholesterol (Technical Group[8]). However, the overlap in cholesterol values led to the conclusion that this test did not predict coronary

lar inference may be drawn from the data reported by Mattingly and associates[6].

Although not age-corrected, it is of interest that a prospective study recently reported indicated a significant increase in the incidence of ischemic heart disease in subjects with serum cholesterol in excess of 275 mg. per 100 ml. of serum (Doyle *et al.*[3]). In our laboratory the same cholesterol value achieved the greatest separation of patients from control subjects in the 4th decade. It is not our intent to imply that a certain cholesterol level will separate normal subjects from patients with coronary heart disease. However, it would seem that the demonstration of a consistent elevation of cholesterol in a young person may well

*The individual cholesterol values for the 4 control subjects in this age group who had values above 275 mg. per 100 ml. of serum were 283, 292, 293 and 295. For comparison, the individual cholesterol values for the 5 coronary subjects who had values below 275 mg. per 100 ml. of serum were 108,196, 241, 244, and 273.

provide information with respect to the likelihood of future coronary attacks.

On the basis of these considerations, and our conviction that early prophylaxis of coronary sclerosis will prove most effective, it is suggested that younger subjects should be given prime consideration in further studies of cholesterol in relation to coronary disease. It should be re-emphasized that although the findings of this study may prove of some practical usefulness in the interpretation of serum cholesterol levels, the true value of this determination as a predictor of coronary heart disease awaits more extensive, prospective studies that emphasize subjects under the age of 40.

Summary. Serum cholesterol data from 95 normal male subjects was compared to those obtained from 88 patients with coronary heart disease for the purpose of evaluating differences in relation to age. It was observed that the greatest difference between mean cholesterols from these 2 groups was in the youngest (4th) decade and that this difference diminished with increasing age through the 6th decade. Not infrequently the serum cholesterol determination is included in routine or screening examinations of older male subjects. Our data suggest that the interpretation of elevated values, with respect to the prediction of coronary heart disease, may be more meaningful in subjects under the age of 40.

TABLE 2.—SUMMARY OF DATA REPORTED BY LAWRY AND ASSOCIATES[5] COMPARING AGE AND SERUM CHOLESTEROL VALUES IN CONTROL SUBJECTS AND PATIENTS WITH CORONARY HEART DISEASE*

	Age 30–39		*Age 40–49*		*Age 50–59*	
	Control	*C.H.D.*	*Control*	*C.H.D.*	*Control*	*C.H.D.*
Number of subjects	294	30	686	119	357	151
Mean serum cholesterol level (mg. per 100 ml.)	228	284	241	273	245	262

Abbreviation: C.H.D. is coronary heart disease.

*In this report data from patients with myocardial infarction and angina pectoris were tabulated separately. These have been combined under a single category by taking weighted means of the cholesterol values.

ACKNOWLEDGMENT: We are indebted to Dr. Clayton B. Ethridge for helpful suggestions in the preparation of this manuscript.

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SUMMARIO IN INTERLINGUA

Le Cholesterol del Sero in Masculos Normal e in Masculos con Morbo Coronario-Cardiac: Differentias con Respecto al Etate

Datos relative al cholesterol del sero in 95 normal subjectos mascule esseva comparate con correspondente datos in 88 patientes con morbo coronario-cardiac, con le objectivo de evalutar le differentias in relation al etate. Esseva constatate que le differentia le plus marcate inter le valores medie de cholesterol in le duo gruppos occurreva in le gruppo de etate del plus juvene, i.e. del quarte decennio e que iste differentia declinava con le avantiamento del etate usque al sexte decennio.

Non infrequentemente, determination del cholesterol del sero es includite in examines de routine o examines serial de detection in le caso de subjectos mascule de etate plus avantiate. Nostre datos suggere que le interpretation de elevate valores—ab le puncto de vista del prediction de morbo coronario-cardiac—es forsan plus significative in subjectos de etates de infra 40 annos.

CEREBRAL HEMODYNAMICS OF SYNCOPE*

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The common denominator in all cases of hemodynamic syncope is acute reduction of cerebral blood supply. Most considerations of this disorder have been chiefly concerned with the causes of, and compensatory mechanisms protecting against, hypotension and reduction of cardiac output. In the final analysis, the induction of syncope must depend upon a diminution of cerebral oxygen delivery to those brain areas concerned with consciousness and must be sufficiently precipitous so as not to be adequately compensated by homeostatic mechanisms. The present report is concerned with studies of cerebral hemodynamics in 8 patients subject to syncope due to orthostatic or postural hypotension.

Method. In all cases, control observations of cerebral blood flow, cerebral vascular resistance, cerebral arteriovenous oxygen difference, cerebral oxygen delivery, cerebral oxygen consumption and mean arterial pressure were made with the subjects in the supine position. They were then tilted (head up) 30 degrees and so maintained for 3.5 to 42.0 minutes, until signs and symptoms of cerebral ischemia became manifest. (Previous observations of these patients' hemodynamic response to tilt, with monitoring of blood pressure, made it possible to predict the probable time of occurrence of cerebral ischemia.) When any of the well-recognized signs or symptoms became manifest, blood samples were drawn quickly since experience has indicated that progression to loss of consciousness occurs within minutes; in fact, all of these subjects developed syncope either during or immediately after the blood specimens were obtained. Cerebral blood flow, cerebral oxygen delivery, and cerebral vascular resistance were again determined, based upon measurement of the cerebral arteriovenous oxygen difference and the mean arterial blood pressure, assuming cerebral oxygen consumption to have remained constant, as has been suggested by previous studies in which hypotension was induced with ganglionic blocking agents (Finnerty, Witkin and Fazekas[6]).

Determination of cerebral hemodynamics and oxygen consumption were made by Scheinberg and Stead's modification[10] of the Kety and Schmidt nitrous oxide procedure[8]. Blood gases were determined by the manometric technique of Van Slyke and Neill[9], and mean arterial blood pressure was obtained directly from the femoral artery by means of a damped aneroid manometer (Alman and Fazekas[1]). During tilt, the latter reading was corrected for hydrostatic effect, depending on tilt angle and relative specific gravities of blood and mercury.

Results. Table 1 presents the data obtained in the cerebral hemodynamic studies of these subjects, assuming, as previously mentioned, the cerebral oxygen consumption to have been maintained under the conditions of the experiment.

The supine or control cerebral blood flow ranged from 35.9 to 60.3, with a mean of 50.0 ml. blood/100 gm. brain/min. The calculated values during

*This investigation was supported in part by a research grant (PHS B-2550) from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

head-up tilt at the time of appearance of symptoms premonitory of syncope ranged from 20.9 to 39.8 ml. blood/100 gm. brain/min., with a mean value of 27.9. The changes are statistically significant.

The control values for mean arterial pressure varied between 75 and 156 mm. Hg with an average value of 101 mm. Hg. The experimental procedure induced blood pressure reduction to levels varying between 11 and 49 with an average of 26 mm. Hg.

The mean value for cerebral vascular resistance when the subjects were supine was 2.1 mm. Hg/ml. blood/100 gm. brain/min., the range being 1.5 to 3.5. There was a consistent fall during tilt to a range between 0.4 and 2.0, with a mean of 1.0 mm. Hg/ml. blood/100 gm. brain/min.

The table demonstrates a frequent change in arterial carbon dioxide content during the experimental procedure; the control values varied between 29.8 and 55.5 vol.% with a mean of 44.5 vol.%. The experimental values, which showed a greater or lesser decrease in 4 of the 8 determinations, varied between 27.8 and 56.5 vol.% with a mean of 43.2 vol.%. Although such changes have no statistical significance as related to any trend in this series, their possible physiological importance will be mentioned.

Table 2 presents the cerebral oxygen changes induced by the experimental procedure. The arterial oxygen content during the control phase varied from 11.29 to 14.43 vol.%, depending largely upon the hemoglobin content. The mean value was 12.50 vol.%. The experimental values were not significantly different, the mean being 12.78 vol.%.

The cerebral venous oxygen content in the control state ranged from 5.78 to 9.39 vol.% with a mean of 7.03 vol.%. Upon the development of presyncopal symptoms, there was a marked fall to values between 1.14 and 4.22 vol.% with a mean of 2.87 vol.%.

The cerebral arteriovenous oxygen difference with the subjects supine varied between 4.23 and 7.05 vol.%, the mean being 5.46 vol.%. With the devel-

TABLE 1.—CEREBRAL HEMODYNAMICS DURING PRESYNCOPE AND SYNCOPE

Age (Yrs.)	CBF		MAP		CVR		Art. CO_2	
	C	E	C	E	C	E	C	E
79	47.7	25.6	75	13	1.6	0.5	44.7	41.1
69	44.9	20.9	156	32	3.5	1.5	29.8	27.8
54	46.0	24.5	94	49	2.0	2.0	44.7	39.3
69	54.5	29.0	97	11	1.8	0.4	54.4	52.0
46	60.3	39.8	110	25	1.8	0.6	46.4	47.4
70	35.9	21.2	96	41	2.7	1.9	32.2	33.7
48	50.2	33.0	88	15	1.8	0.5	48.3	48.2
62	60.1	29.0	91	21	1.5	0.7	55.5	56.5
			Mean Values					
62	50.0	27.9*	101	26*	2.1	1.0*	44.5	43.2

*Significant difference, $p<.01$

CBF indicates cerebral blood flow in milliliters per minute per 100 gm. brain; MAP, mean arterial blood pressure in millimeters Hg; CVR, cerebral vascular resistance in millimeters Hg per milliliter of blood per minute per 100 gm. brain; Art. CO_2, arterial carbon dioxide content in volumes %; C, control, and E, experimental.

opment of early cerebral ischemia, these values were found to vary between 7.04 and 12.74 vol.% with a mean of 9.91 vol.%, a significant change.

Cerebral oxygen delivery in the control state ranged between 4.1 and 8.7, with a mean value of 6.3 ml. oxygen/100 gm. brain/min. Primarily as a result of the reduction of cerebral blood flow during the experimental procedure, these values fell to 2.7 to 4.5, the mean being reduced to 3.5 ml. oxygen/100 gm. brain/min.

TABLE 2.—CEREBRAL OXYGEN CHANGES DURING PRESYNCOPE AND SYNCOPE

Age (Yrs.)	CBF		Art. O_2		Ven. O_2		$CAVO_2$		$CMRO_2$	CDO_2	
	C	E	C	E	C	E	C	E		C	E
79	47.7	25.6	12.14	13.02	7.40	4.03	4.74	8.99	2.3	5.8	3.3
69	44.9	20.9	13.62	13.09	9.39	4.00	4.23	9.09	1.9	6.1	2.7
54	46.0	24.5	12.55	13.66	6.54	2.25	6.01	11.41	2.8	5.8	3.3
69	54.5	29.0	11.52	11.13	6.14	1.14	5.38	9.99	2.9	6.3	3.2
46	60.3	39.8	11.51	11.26	6.83	4.22	4.68	7.04	2.8	6.9	4.5
70	35.9	21.2	11.29	13.66	5.78	4.22	5.51	9.44	2.0	4.1	2.9
48	50.2	33.0	12.91	12.30	5.86	1.70	7.05	10.60	3.5	6.5	4.0
62	60.1	29.0	14.43	14.13	8.32	1.39	6.11	12.74	3.7	8.7	4.1
					Mean Values						
62	50.0	27.9*	12.50	12.78	7.03	2.87*	5.46	9.91*	2.7	6.3	3.5*

*Significant difference, $p<.01$

CBF indicates cerebral blood flow in milliliters per minute per 100 gm. brain; Art. O_2, arterial oxygen content in volumes %; Ven. O_2, venous oxygen content in volumes %; $CAVO_2$, cerebral arteriovenous oxygen difference in volumes %; $CMRO_2$, cerebral oxygen consumption in milliliters per minute per 100 gm. brain; CDO_2, cerebral oxygen delivery in milliliters per minute per 100 gm. brain; C, control, and E, experimental.

Discussion. Although the term "syncope" is often loosely defined, we are concerned primarily with those disorders characterized by sudden loss of consciousness of hemodynamic origin. In such states, it is generally agreed that syncope is due to an acute impairment of energy production consequent upon interference with the oxygen supply of the brain, at least to those cerebral areas concerned with consciousness. To our knowledge, no other substrate is in such critical supply that a comparably brief deprivation will result in functional disturbance. Since the brain is, for practical purposes, an aerobic organ wholly dependent upon the circulating blood for its oxygen supply, any reduction of cerebral oxygen delivery below the critical values for maintenance of normal function in those cerebral areas concerned with consciousness must be related to a decrease in arterial oxygen content or a decrease in cerebral blood flow (or an exceedingly improbable increase in cerebral oxygen consumption). Three of the subjects of the present study actually demonstrated a slight increase in arterial oxygen content prior to syncope (this, as will be noted, doubtless due to hyperventilation); in the remainder, any reduction in arterial oxygen content was negligible. Therefore, the clinically evident decrease in cerebral oxygen delivery must be attributed to reduction in cerebral blood flow. Indeed, the calculated cerebral blood flow during the experimental phase in

all cases demonstrated a significant reduction. It should be pointed out that, according to the basis of calculation used in the experimental portion of this study, if there were an appreciable reduction of cerebral oxygen consumption as the result of cerebral ischemia, the increased arteriovenous oxygen differences which were demonstrated would have to be accounted for by even greater decreases in cerebral blood flow than are presented. However, it is interesting to note that among almost all of the present cases, there is fairly good agreement with respect to the level of cerebral blood flow (approximately 25 to 30 ml. blood/100 gm. brain/min.) at which signs of cerebral ischemia became evident, such flow rates having been calculated with the assumption that cerebral oxygen consumption was unchanged. This rather narrow range corresponds to that obtained in previous studies in which there was actual measurement of cerebral oxygen consumption, which was shown not to have undergone a demonstrable reduction during unconsciousness due to pharmacologically-induced hypotension (Finnerty, Witkin and Fazekas[6]). The relative constancy of this "critical level" would seem to indicate that it represents the overall cerebral blood flow rate at or immediately below which those brain areas concerned with consciousness can no longer receive their required minimum oxygen supply. The low value of the "critical level" represents the existence of a rather wide margin between the normal rate of cerebral blood flow and the rate at which symptoms of cerebral ischemia develop.

There can be no doubt, of course, that progressive reduction of blood pressure below critical levels must result in reduction of cerebral oxygen delivery and, hence, of utilization. The latter is ultimately limited by the amount of oxygen which can diffuse from the arterial blood supply (that is, to the extent that the cerebral venous oxygen may approach zero and, in fact, as can be seen from the present data, may fall to extremely low levels). However, in 4 subjects, the cerebral venous oxygen content was approximately 4 vol.%. Since in the remaining 4 subjects, this value ranged between 1.14 and 2.25 vol.%, it becomes necessary to examine the possible reasons for development of cerebral ischemia in some cases at a time when cerebral oxygen delivery apparently was not being completely utilized. It seems highly probable that unconsciousness in such instances may, nevertheless, have been due to localized inadequacy of cerebral oxygen delivery, while much of the brain was more than minimally supplied.

There are two alternative possibilities which should be noted in connection with the previous demonstration (Finnerty, Witkin and Fazekas[6], Scheinberg and Stead[10]) that early or mild degrees of cerebral ischemia are not associated with demonstrable reduction in overall cerebral oxygen consumption. The first of these is that those brain areas responsible for the earliest manifestations of cerebral ischemia may represent a sufficiently small proportion of the total cerebral tissue so that diminution in their oxidative metabolism may not be discernible by a method which measures the average oxygen consumption of the entire brain. Secondly, it has been pointed out that the oxygen requirements for manifest cerebral function may be so small that reduction in oxygen consumption sufficient to produce dysfunction may be obscured, so far as a relatively insensitive technique is concerned, by the large oxygen requirements of cerebral vegetative metabolism (Fazekas, Alman and Bessman[4]).

A third consideration applicable to the present study involves the vasoconstrictor effects of hyperventilation on the cerebral vasculature (Fazekas *et al.*[5], Kety and Schmidt[7]), hyperpnea having been present in several cases as revealed by a decrease in arterial carbon dioxide content or an at least small increase in arterial oxygen saturation. The incidence and extent of hypocapnia may not even have been fairly demonstrated, since blood specimens may well have been obtained before or after the time of maximal blood gas concentration change. Clinically, it is a familiar observation that hyperventilation is a frequent accompaniment of anxiety and apprehension, which may in some cases be considered manifestations of cerebral ischemia. Previous studies have demonstrated that only one or two deep respiratory cycles can significantly reduce arterial carbon dioxide content (Dickinson[3]). Our own investigations have demonstrated that very short periods of active hyperventilation (1 to 2 minutes) can, by increasing cerebral vascular resistance, reduce cerebral blood flow by as much as 40%[5]. Synthesis of these observations suggests that syncope of many apparently obvious origins may be precipitated by unnoticed hyperventilation. A similar suggestion was made by Burnum, Hickam and Stead[2] who, however, directed their attention to the effects of hyperventilation in potentiating postural hypotensive states; this view had also been expressed previously by Stead[11]. Recently we have had the opportunity to observe dramatic and rapid improvement of clinical and cerebral hemodynamic status of several patients with vasovagal syncope upon the inhalation of 5% carbon dioxide and 95% oxygen.

The rather marked variations in mean arterial pressure levels at which signs of cerebral ischemia may become manifest deserve some comment. It is apparent from the above and other considerations that the critical value for mean arterial pressure will be dependent upon the cerebral vascular resistance. If a marked compensatory reduction of cerebral vascular tone is possible, then critical values for mean arterial pressure may be extremely low. If, however, vascular tone is increased by an only small extent, then relatively slight reduction in pressure, of whatever origin, may induce syncope.

Summary and Conclusions. In 8 patients subject to hypotension and syncope, cerebral hemodynamic studies were performed in the supine position and during head-up tilt, when signs and symptoms of cerebral ischemia appeared. Immediately prior to syncope, there was a marked fall in mean arterial pressure, cerebral blood flow, oxygen delivery, and venous oxygen content. There was a widening of the arteriovenous oxygen difference, which was assumed to be due entirely to reduction in cerebral blood flow on the basis of previous studies. The cerebral vascular resistance fell consistently. In 4 of the 8 patients, there was a greater or lesser decrease in arterial carbon dioxide content, most likely due to hyperventilation preceding syncope.

The consistency with which clinical evidence of cerebral ischemia appeared at cerebral blood flow rates of approximately 30 ml./100 gm. brain/ min. suggests that, in the majority of cases, at or immediately below this "critical" flow rate, those cerebral areas concerned with consciousness can no longer receive their required minimum blood flow. The blood pressure at which this occurs may vary, depending upon cerebral vascular resistance.

The finding of persistence of significant levels of oxygen in the cerebral venous blood during cerebral ischemia indicates that the symptoms may be

due primarily to oxygen deprivation maximal in relatively small brain areas. In some cases, this may be related to the hypocapnia of hyperventilation so that syncope may perhaps be precipitated by the cerebral effects of overbreathing, superimposed upon acute hypotension.

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SUMMARIO IN INTERLINGUA

Hemodynamica Cerebral de Syncope

Esseva effectuate studios del hemodynamica cerebral in 8 patientes subjecte a hypotension e syncope. Le patientes esseva in decubito dorsal e in position inclinate con le capite in alto quando signos e symptomas de ischemia cerebral comenciava manifestar se. Immediatemente ante le syncope il occurreva un marcate reduction del tension arterial medie, del fluxo de sanguine cerebral, del livration de oxygeno, e del contento venose de oxygeno. Se augmentava le differentia arterio-venose de oxygeno. Isto—super le base de previe studios—esseva interpretate como integremente causate per le reduction del fluxo de sanguine cerebral. Le resistentia cerebro-vascular declinava uniformemente. In 4 del 8 patientes, un plus o minus marcate reduction occurreva in le contento arterial de bioxydo de carbon. Isto esseva le plus probabilemente le effecto de hyperventilation ante le syncope.

Le regularitate con que evidentia clinic de ischemia cerebral se declarava con fluxos de sanguine cerebral de approximativemente 30 ml per 100 g de cerebro per minuta suggere que in le majoritate del casos, il occurre a o infra ille nivello "critic" del fluxo que le areas concernite con conscietate pote non plus obtener lor requirimento minimal de fluxo de sanguine. Le tension de sanguine al qual ille evento occurre pote variar in dependentia del resistentia cerebro-vascular.

Le constatation del persistentia de significative nivellos de oxygeno in le sanguine cerebro-venose durante ischemia cerebral indica que le symptomas es possibilemente causate in le prime loco per un privation maximal de oxygeno in relativemente micre areas cerebral. In certe casos, isto es forsan relationate con le hypocapnia de hyperventilation, de maniera que le syncope es possibilemente precipitate per le effectos cerebral de excessos de respiration in superimposition a hypotension acute.

T WAVE ABNORMALITIES IN PATIENTS WITH NO EVIDENT HEART DISEASE: THE EFFECT OF POSTURE*†

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The electrocardiographic diagnosis of heart disease is subject to error when T wave abnormalities alone are present. Many authors have cautioned against over-interpretation of such changes, stressing the great number of non-pathologic factors which influence this portion of the tracing (Graybiel *et al.*[7], Hyman[13], Littman[14], Marriott[18], Rosen and Gardberg[22], Seldon[29], Sensenbach[30], Wendkos[34]). In other cases, T wave abnormalities may certainly be indicative of heart disease and even herald an impending myocardial infarction (Greene and Kelly[8], Mangold and Borter[17], Pruitt, Klaheg and Chapin[20], Schlant, Levine and Bailey[27]).

We became interested in this problem because of our experience with 14 patients who had unexplained T wave abnormalities. In each instance marked lability of the ST-T portion of the tracing was demonstrable by a variety of physiologic and pharmacologic maneuvers. From the beginning we were impressed with the changes produced in these patients by taking the electrocardiogram in the erect position. We elected, therefore, to study the effect of the standing position on the ST-T segments of a group of healthy subjects. This report will outline our experience with these 2 groups of individuals.

Methods. For the purposes of this study a normal electrocardiogram was considered to be one in which the following criteria were met (New York Heart Association, 1953): 1) Absence of abnormalities of the P wave and QRS complexes except for well accepted variations of normal such as incomplete right bundle branch block. 2) Upright T waves of at least 1 mm. in I and II. 3) Upright T waves of at least 1 mm. in aVf. 4) Upright T waves of at least 2 mm. in the precordial leads from the transition zone leftward.

There were, first of all, the 14 original patients whose electrocardiograms had failed to meet these criteria because of abnormalities of the T wave. They had been selected for study because a thorough history and physical examination, as well as indicated laboratory studies, failed to reveal evidence supporting a diagnosis of organic heart disease.

The control group consisted of 74 patients ranging in age from 16 to 53. They were free of heart disease as far as could be determined by history and physical examination. The group consisted of 58 white males, 15 white females, and one Negro male.

The electrocardiographic tracings included the standard 12 leads. The recumbent tracings were taken first, and followed immediately by the erect tracings. The usual care was taken to assure that the precordial leads were taken from identical spots on the chest wall in both positions. All of the patients in both groups had at least one set of complete electrocardiograms, one taken in

*The views expressed in this paper are those of the authors and do not represent a statement of official policy of the United States Navy.

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TABLE 1.—FINDINGS IN EACH OF THE 14 PATIENTS WITH ABNORMAL RECUMBENT ELECTROCARDIOGRAMS.

			Change				*	†	
		Age	*Erect Rate*	*Rate*	*PR*	*QT*	*Elec. Pos.*	*Trans. Zone*	*T Waves*
Group I 38 pts.	Range	16–53	55–105	−5/+30	+0.01/−0.02	0/−0.04	O/→V	O/L2	
	Mean	24	90	+10	0	−0.02	0	0	none
Group II 25 pts.	Range	18–47	80–125	0/+45	+0.01/−0.04	0/−0.08	O/→V	O/L1½	II, III flattened—13 aVf, V6 flattened—18 all others—once or more
	Mean	32	90	+20	0	−0.02	0	L½	
Group III 11 pts.	Range	18–44	65–105	+5/+40	0/−0.04	0/−0.06	O/→V	R½/L1	II, aVf inverted—10 V6 inverted—2 V4–5 inverted—1 other leads generally flat
	Mean	25	95	+20	−0.02	−0.04	0	L½	
Group IV 11pts.	Range	19–45	80–125	0/+55	0/−0.08	0/−0.08	H/→V	O/L½	I decreased—8 II decreased—10 III decreased—8 aVf decreased—12 Other chest leads decreased—5
	Mean	30	100	+15	−0.01	−0.02	O	L½	

*O means that electrical position stayed within the same range as defined by the terms horizontal, semihorizontal and others.
→V means that the electrical position shifted towards the vertical position, for example, from intermediate to semivertical.
†O means that no shift in the transition zone occurred.
L means that the transition zone shifted leftward on the chest wall. One unit of shift is considered to be the equivalent of one position, for example, from V_3 to V_4
R means that a shift in the transition zone toward the right on the chest wall occurred.

the recumbent position and one in the erect. Each set of tracings was then analyzed for the following factors: 1) Rate in the erect position. 2) Change in rate on assuming the erect position. 3) Change in PR interval. 4) Change in QT interval. 5) Change in electrical position. 6) Change in transition zone.

Some of the patients with abnormal recumbent tracings were selected for special experiments. Four of those whose electrocardiograms "deteriorated" on standing were given 0.5 mg. of ergotamine tartrate intramuscularly after obtaining a set of control electrocardiograms. Each of these patients developed nausea within a half hour. This time interval was selected for taking the second set of tracings. One patient whose abnormal electrocardiogram reverted to normal on standing was also tested in a similar manner with ergotamine. Five of the patients whose electrocardiograms became worse on standing were studied after administering phentolamine in doses of 5 or 10 mg. either intravenously or intramuscularly. The leads in which the most marked changes occurred on standing in the control set were then repeated in the standing position every 5 minutes for a total of 30 minutes.

Three of the patients who showed more marked inversion of the T waves in the standing position were also tested for their response to hyperventilation and exercise. Once again the lead in which the most marked change in the erect position occurred was selected for study. The patients were requested to hyperventilate with the electrocardiograph running. Twenty seconds of hyperventilation was sufficient to produce changes in each instance. Following "recovery" of the T waves to the control pattern each patient was requested to perform 15 situps as fast as possible. Immediately after completion of the exercise another strip of the same lead was obtained in the recumbent position.

Three of the 14 patients with abnormal recumbent electrocardiograms demonstrated a marked return toward normal in the erect position. Two of these were selected for special study. After obtaining the control set of tracings, one patient was given 0.6 mg. of atropine sulphate intramuscularly and one 15 mg. of probanthine intramuscularly. Another complete set of tracings was obtained 30 minutes after the injection in each instance.

TABLE 2.—ELECTROCARDIOGRAPHIC CHANGES IN RESPONSE TO POSTURE

Electrical Position	*Group I*	*Group II*	*Group III*	*Group IV*
H	3	2	0	0
SH	3	1	0	0
I	13	8	1	3
SV	7	7	3	4
V	12	8	7	4
Transitional Zone				
V_2	2	0	2	0
V_{2-3}	4	1	3	2
V_3	3	3	3	4
V_{3-4}	12	11	1	3
V_4	12	5	0	1
V_{4-5}	4	6	2	1
V_5	0	0	0	0
V_{5-6}	1	0	0	0

Results. The electrocardiograms of the control subjects could be divided into 3 groups depending on the response to postural change. The first consisted of 38 patients in whom the electrocardiogram remained within the limits of normal, although minor T wave changes sometimes occurred. Twenty-five patients demonstrated abnormal T wave flattening with or without inversion of TIII. Eleven patients developed T wave inversion in leads other than III. As mentioned previous-

TABLE 3.—ELECTRICAL POSITION AND TRANSITION ZONE IN THE CONTROL GROUPS AND IN THOSE WITH ABNORMAL RECUMBENT ELECTROCARDIOGRAMS BECOMING MORE ABNORMAL ON STANDING.

Patients with Abnormalities Accentuated by Erect Position

	Age	*Sex*	*Race*	*Erect Rate*	*Change in Rate*	*Change in R–R*	*Change in Q–T*	*Elec Pos*	*Trans Zone*	*Recumbent Tracing*	*SST Changes*	*Comments*
1	19	M	Wh	80	0	—0.02	—0.02	V/O	V_3/V_{3-4}	III Inverted AV_F Flat	AV_F Inverted V_6 and II Flat	Young male with mild anxiety Standing reproduced original abnormality Exercise and hyperventilation also caused changes
2	33	F	Wh	95	+5	0	—0.01	SV/I	V_{3-4}/V_4	Normal	I,II, aV_F and V_6 Flat	Mild labile hypertension Standing reproduced original abnormality
3	31	M	Wh	100	0	—0.04	+0.02	SV/O	V_{4-5}/O	Flat T in I and V_6	T inverted in I and V_6	Diabetes mellitus and hyperthyroidism No evidence of heart disease
4	30	F	Wh	105	+25	—0.01	—0.02	V/O	V_{3-4}/V_4	Normal	Flat T, depressed ST in II, III, aV_F and V_5 and V_6	Upper respiratory infection Standing reproduced original abnormality
5	27	M	Wh	135	+55	—0.05	—0.08	V/O	V_4/O	T flat in I, V_5 and V_6. Inverted T V_{1-4} ("Juvenile Pattern")	T inverted in II, III, aV_F and V_6. But upright V_{1-4}	Anxiety and hyperventilation. "Juvenile pattern" abolished by standing while abnormalities were accentuated elsewhere.
6	33	M	Wh	100	+10	0	—0.04	SV/O	V_3/V_{3-4}	Flat T in I Inverted II, III, aV_F, V_{5-6}	Markedly inverted in I, II, III, aV_F V_{5-6}	Anxiety. Standing accentuated original findings. Ergot corrected changes.
7	28	M	Wh	85	+20	0	—0.02	SV/V	V_{3-4}/V_4	Normal—Junctional ST elevation in II, V_{4-5}	T inverted III, aV_F. Notched and Flattened II, V_6	Anxiety and hyperventilation during influenza. Exercise test negative. Ergot corrected changes. Standing reproduced original changes.
8	22	F	Wh	100	+10	—0.02	—0.02	I/SV	$V_2–V_3/O$	T inverted V_4. Flat in	T inverted I, II, III, a V_F, V_6	Anxious patient with inactive pulmonary tubercu-

8	22	F	Wh	100	+10	−0.02	−0.02	I/SV	V_2–V_3/O	T inverted V_5. Flat in V_{5-6}, I	T inverted I, II, III, a V_F, V_6 and deep inversion V_{2-5}	Anxious patient with inactive pulmonary tuberculosis. Syncopal episode during bout of diarrhea. Standing accentuated abnormality. Ergot normalized tracing.
9	29	M	Wh	100	+20	−0.02	−0.04	V/O	V_3/V_{3-4}	Mild T flattening in I, II, III, aV_F and V_{4-6}	Flat T in I, II, III, aV_F, V_2 and V_6. T inverted in V_{3-5}	Duodenal ulcer. Standing accentuated abnormality on 2 occasions. Abnormality not corrected with ergot or regitine.
10	41	M	Wh	105	+15	0	−0.02	I/O	V_3/V_4	Mild T flattening in I, aV_L	Flat T in I, aV_L, V_6.	Patient with narcolepsy, taking dexedrine. Standing accentuated abnormality
11	45	F	Wh	105	+25	0	−0.04	I/O	V_{2-3}/V_3	Mild T flattening V_5 and V_6	Flat T in I and V_5. Inverted in II, III, aV_F, V_6	Anxious patient with systolic hypertension. Original abnormality markedly accentuated by standing, as well as by hyperventilation.
							Patients with Abnormalities Corrected by Erect Position					
12	47	M	Negro	105	+35	−0.02	−0.04	I/O	V_{2-3}/V_3	T inverted in III, V_{3-5}. Flat and notched in I,II, aV_F, V_6	Normal but T in V_2 and V_3. Slightly notched.	Admitted with duodenal ulcer with hemorrhage. Well stabilized when study performed 2 days later.
13	37	M	Wh	100	+15	−0.02	−0.04	I/O	V_{4-5}/V_5	Incomplete RBBB or "Crista" pattern broad S in I, II, V_6. R′ in a V_R. No R′ in V_1. T inverted in II, III, aV_F, V_{4-6}	S appears in III, resembling Crista pattern. T waves normal. Frequent PVCs appear	Routine ECG while hospitalized because post-traumatic encephalopathy. Probanthine partially normalized tracing, did not produce PVCs.
14	41	M	Negro	125	+35	−0.02	−0.04	I/O	V_{2-4}/O	T inverted in I, II, aV_L, aV_F, V_5 and V_6. Flat T III.	Normal	Functional heart murmur. Atropine also normalized tracing.

I, SV, V, refer to Intermediate, semivertical and vertical electrical positions. Figures to the right of the slant indicate direction of axis shift, if any, on assuming the erect position.

ly, the patients with abnormal recumbent electrocardiograms could be divided into 2 distinct categories. Eleven demonstrated marked worsening of the T wave changes on standing, and 3 reverted to a much more normal pattern. Table 1 lists the mean values, ranges, and T wave changes which occurred in each of the groups studied. No data are listed, however, for the group whose abnormal tracings became normal on standing because of the small number of patients with this type of response. The electrical position and location of the transition zone in the recumbent tracings for the same groups are summarized in Table 2.

Table 3 lists the data for each of the 14 patients with abnormal recumbent electrocardiograms. The following case reports will briefly illustrate the influence of posture on 2 of these:

CASE 6 (Table 3), a 33-year-old white man, was admitted to the hospital because of an abnormal electrocardiogram (Fig. 1*a*) and atypical chest pain. Thorough history and physical examination failed to reveal any evidence of heart disease. Laboratory studies, including an exercise test performed almost to tolerance, were within normal limits except for the electrocardiogram which per-

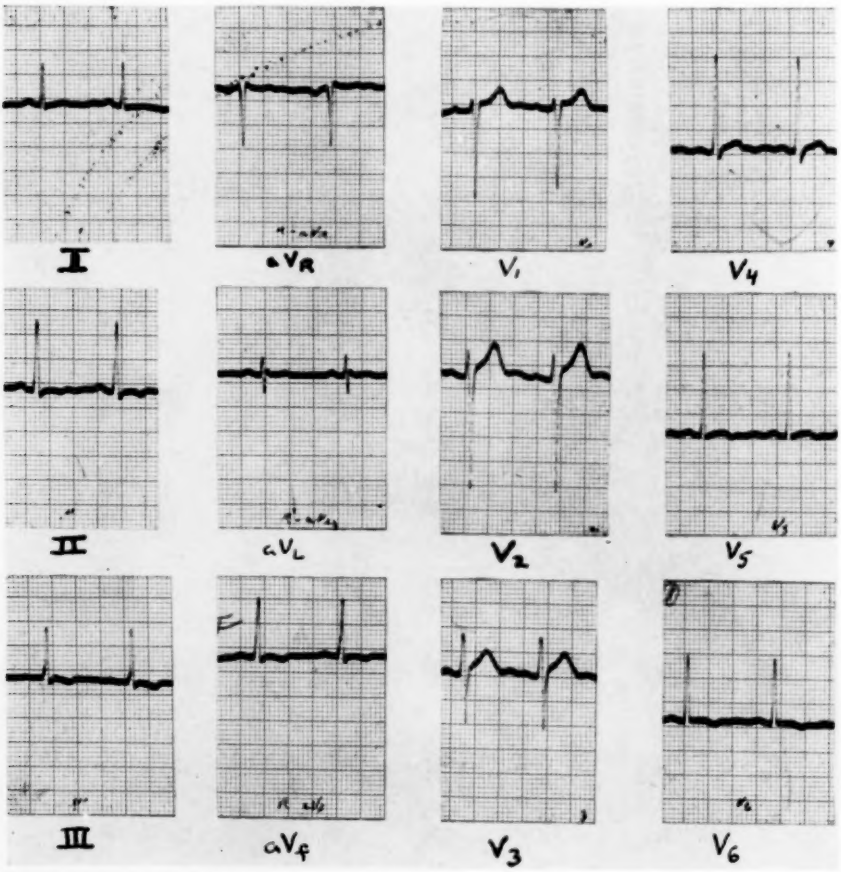

Fig. 1*a*—Recumbent electrocardiogram (Case 6, Table 3).

sisted in showing generalized flattening of the T waves. A tracing taken in the erect position revealed marked accentuation of the abnormalities (Fig. 1*b*), and it was concluded that these ST-T changes were similar to those described by Wendkos in 1944 and were not indicative of heart disease[34].

CASE 14 (Table 3), a 41-year-old Negro male, was admitted to the urologic service because of prostatic obstruction. His physician heard a murmur and ordered an electrocardiogram (Fig. 2*a*). He was seen in consultation, and the only detectible abnormality in the history or physical examination was a very soft, grade one, basal systolic murmur. The erect position produced a return to normal (Fig. 2*b*), and it was concluded that this patient likewise had T wave inversion of no pathologic significance.

The patients to whom ergotamine was given reacted in the following fashion: Three of the 4 whose abnormal recumbent tracings became worse on standing had reversal of these changes and little or no "deterioration" in the erect position. The other patient

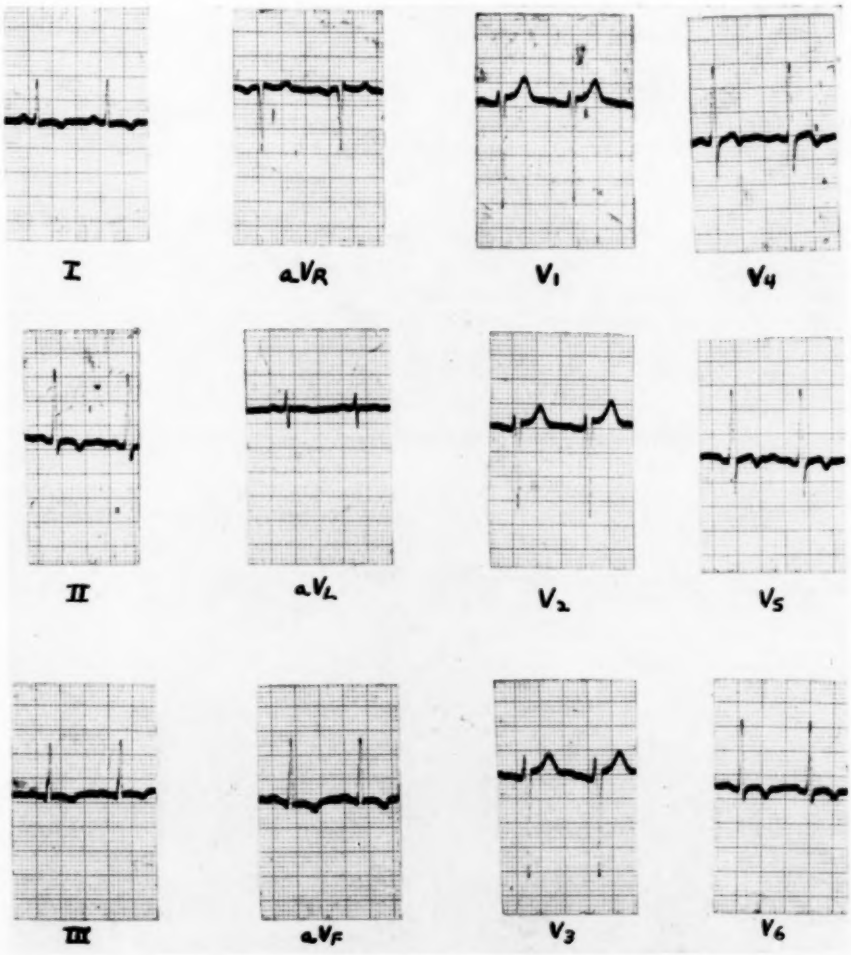

Fig. 1*b*.—Erect electrocardiogram of the patient in Fig. 1*a*. Note the response of the T waves particularly in Leads I, II, aV_F, and V_{4-6}.

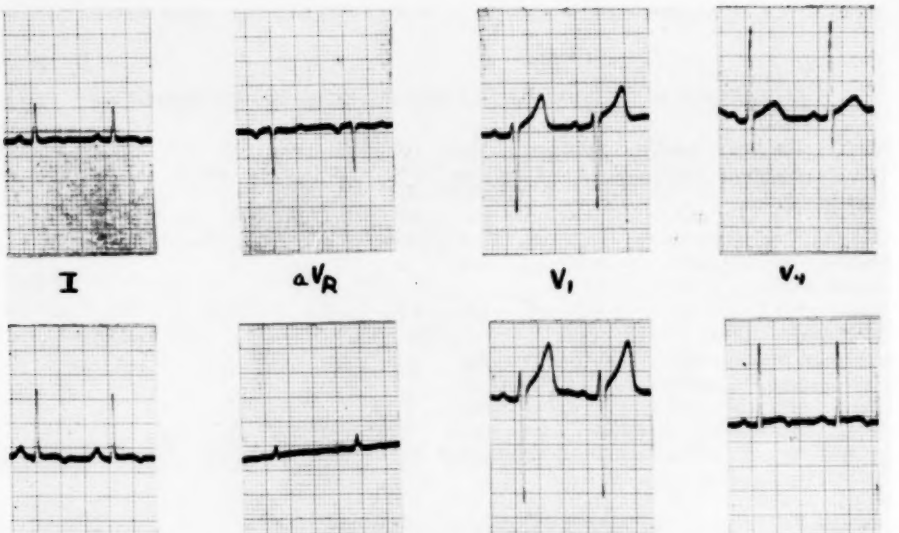

Fig. 2*a*.—Recumbent electrocardiogram (Case 14, Table 3).

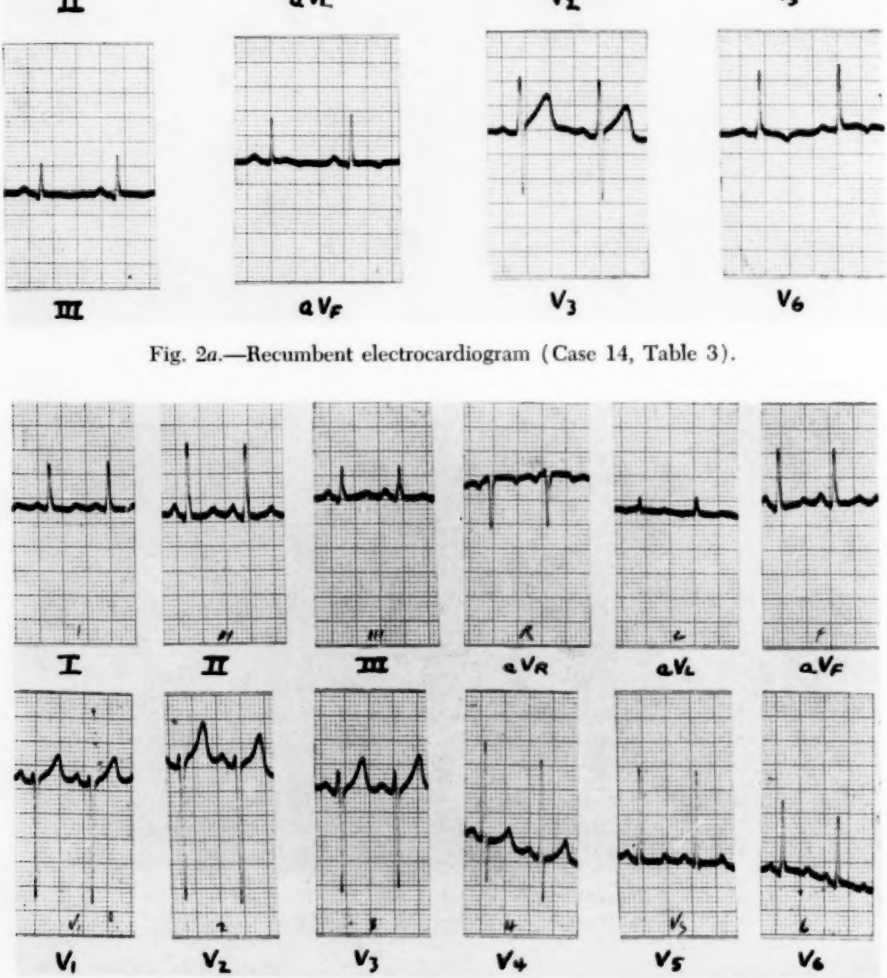

Fig. 2*b*.—Erect electrocardiogram of the patient in Fig. 2*a*. Note the marked return of the T waves to the normal direction. The rate has increased from 90 to 125.

had no electrocardiographic response. The one patient whose recumbent tracing was reverted to normal on standing developed increased inversion of the T waves with no improvement on standing.

Phentolamine produced no important changes in the electrocardiograms of the patients to which it was administered.

The 3 patients who were tested for response to hyperventilation and exercise all responded with increased T wave inversion of the same type seen in their erect tracings.

The recumbent electrocardiograms of the patients given atropine and probanthine were much improved.

T wave inversion or flattening occurred most frequently in leads II, III, aVf and V6, although no lead was exempt. Usually there was inversion of the proximal portion of the T wave accompanied by a terminal positive phase and an early take-off of the T-P segment. A few patients, however, had symmetrical T wave inversion. In 5 tracings the elevation of the T-P segment resulted in an illusory S-T segment depression of 0.5 to 1 mm. In general, the changes occurred most often in patients with vertical or semivertical mean QRS axes, although there were many patients with similar axes who exhibited no change, and others with intermediate axes who did develop T wave abnormalities. There were, however, only 3 patients with horizontal or semihorizontal axes who exhibited these changes. Upon assuming the erect position the QRS vector either did not change or shifted toward the vertical in the frontal plane and to the posterior in the horizontal plane. On the other hand, the T wave vector tended to shift to a more superior and anterior direction. The net result of these changes was a widening of the QRS-T angle. Subjects who, upon assuming the erect position, demonstrated T wave changes usually had a somewhat greater increase in rate than those who did not; however, only a few individuals developed sinus tachycardia, and some showed no change in rate. Factors unrelated to the appearance of the T wave changes were: location of the transition zone, changes in the PR and QT intervals, age, and sex.

Discussion. The cause of orthostatic T wave inversion and flattening has been the subject of much investigation (Mayerson and Davis[19], Rosen and Gardberg[22,23], Scherf and Weissberg[26], Sigler[31], Wendkos[34], Ylvisaker and Kirkland[38]). From our studies several possibilities at least can be discarded.

The erect rate and the increase in rate on standing do not seem to be of importance. First, there was almost no difference in the mean erect rates among the 3 groups of healthy controls. Second, only a few patients developed sinus tachycardia. Some of these demonstrated T wave changes, and others did not. Third, some patients who developed orthostatic T wave changes showed no change in rate whatsoever. Thus, while orthostatic T wave changes may be associated with factors tending to increase the rate, we do not believe that these changes are due to increments in rate *per se*.

A simple anatomical or electrical reorientation of the heart within the thorax does not explain the T wave changes observed. If this were so, the QRS and T axes ought to shift in the same direction in response to changes of position. An analysis of the axis shifts encountered in this study revealed a widening of the QRS-T angle, thus eliminating simple displacement of the electrical axes as an explanation for the phenomenon of orthostatic T wave inversion.

Latent heart disease is also an un-

likely explanation for the T wave changes noted in this study. The large number of healthy young persons who responded to the erect position with T wave inversion seems to rule out this factor. Rosen and Gardberg[22,23] reached similar conclusions. A number of their patients exhibited T wave changes in the standing position, as well as under a variety of other circumstances such as exercise, smoking, and hyperventilation. They calculated the ventricular gradients and found that none of these stimuli caused a change in its direction. On the other hand, when myocardial disease was responsible for T wave change, the direction of the gradient did change. Many others (Schlant, Levine and Bailey[27], Sigler[31], Wendkos[34], White, Chamberlain and Graybiel[36], Ylvisaker and Kirkland[38]) have concluded likewise that latent heart disease cannot be a likely explanation.

Some authors feel that the abnormalities result from changes of the situation of the heart within the thorax, disturbing its normal contact with highly conductile tissues such as the anterior chest wall, posterior muscle masses, and the diaphragm. Such loss of normal contact would thus make the thorax a poorer volume conductor (Evans and Lloyd-Thomas[5], Scherf and Schlachman[24], Scherf and Weissberg[26], White, Chamberlain and Graybiel[36]). Mayerson and Davis[19] have shown that the T wave changes may progress or improve during continued positional change and, therefore, doubt that the original variations can be explained by this means. Furthermore, QRS changes should be as frequent as T variations if the volume conductor theory is correct. Significant QRS changes were absent in our experiments.

Since sympathetic tone is increased in the erect position, the changes in the electrocardiogram may be somehow mediated through the autonomic nervous system (Horwitz and Graybiel[12], Mayerson and Davis[19], Seldon[29], Sjostrand[32], Wendkos[34]). Evidence for this thesis is based on a variety of experimental observations. Direct stimulation of the cardiac sympathetic nerves will produce ST-T changes in the electrocardiogram (Best and Taylor[2]), as will infusion of minute amounts of epinephrine (Cannon and Sjostrand[3], Hartwell *et al.*[10], Sjostrand[32]). Amyl nitrite has been shown to induce similar changes, presumably as a result of sympathetic response to the vasodilating effects of the drug (Ashman and Byer[1], Sjostrand[32]). It has been shown that the ST-T wave changes produced by the erect position may be blocked by ergotamine tartrate, an adrenergic blocking agent (Wendkos[34], Wendkos and Logue[35]). Clinical studies have revealed the same type of change under a variety of physiologic conditions in which sympathetic tone is increased. A number of reports have stressed the influence of anxiety, a condition in which the "fight or flight" reaction is heightened (Grau[6], Groom[9], Heyer, Winans and Plessinger[11], Loftus, Gold and Diethelm[15], Mainser and Krause[16], Sensenbach[30]). Exercise has been noted also to produce ST-T changes in the absence of cardiac disease (Ashman and Byer[1], Rosen and Gardberg[22,23]). Hyperventilation may mediate its changes through the increase in sympathetic tone produced by the resulting exercise (Scherf and Schlachman[24]), although this is probably not the only factor involved. In this circumstance it is possible that alkalosis potentiates the effect of epinephrine on the tracing (Wendkos[34]).

It is very likely then that autonomic nervous system imbalance with adrenergic predominance, the result perhaps either of chronic anxiety or poor physi-

cal conditioning, is the basic disturbance when patients of the type described develop increasing repolarization abnormality in the erect position. The same basic mechanism is probably operative to a lesser degree when patients with normal recumbent tracings develop change on standing, while hyperventilating, or after exercise.

If autonomic imbalance plays a role in orthostatic T wave change, it would be expected that instances of both increased and decreased tone would be found. We encountered 3 patients with markedly abnormal recumbent tracings who demonstrated a return to normal under circumstances designed to increase sympathetic tone relative to parasympathetic. Standing normalized all 3 tracings (for example, Fig. 2). Two of these patients were given parasympathetic blocking agents with a resultant return toward normal. In one given ergotamine there was an exacerbation of the recumbent abnormalities, and no improvement on standing was noted. The findings in these cases suggest that the changes are due to a diminution of adrenergic, or to an increase in parasympathetic, activity.

There are objections to the concept that changes in sympathetic tone are responsible for orthostatic T wave change. Ergotrate increases the T waves of the normal recumbent electrocardiogram (Hartwell, Burnett and Graybiel[10]), and even results in reversion toward normal of inverted T waves in some patients with heart disease (Scherf and Schlachman[25]). The adrenergic blocking action of ergotrate thus may not necessarily be the factor responsible for the lessening of orthostatic T wave alterations. In an attempt to clarify this, we administered phentolamine, another sympathetic blocking agent, to some of our patients who presumably had increased sympathetic tone. Since we did not observe any tendency toward prevention of orthostatic T wave change with this agent, the mechanism of ergotamine action in this respect remains uncertain.

In summary, although there is strong evidence favoring the hypothesis that orthostatic T wave changes are the result of alterations in sympathetic tone, absolute proof is not available. The concept is, none the less, an exceedingly attractive one.

CLINICAL IMPLICATIONS. It is apparent from the above discussion that a great many physiologic circumstances may be associated with innocent T wave abnormalities. In addition to the previously mentioned factors, smoking (Rosen and Gardberg[22]), ingestion of food (Rochlin and Edwards[21], Sears and Manning[28]), or cold water (Dowling and Hellerstein[4], Wilson and Finch[37]), gastric distention (Marriott[18]), and gallbladder disease (Marriott[18]) have all been reported to be occasionally associated with similar changes. Even serial T wave changes may not indicate disease, therefore, because the physiologic forces which we believe induce these changes may wax and wane. Two of our patients had serial changes with a gradual return to normal over a period of weeks. In each instance the erect position produced a tracing similar to the original abnormal recumbent one.

From a practical standpoint, physicians interpreting electrocardiograms should, in our opinion, avoid a specific diagnosis when T wave flattening or inversion alone are encountered. Such changes should be labeled "nonspecific" and their significance decided upon on the basis of associated clinical circumstances.

If the clinical circumstances do not seem to warrant a diagnosis of heart disease, reassurance for both patient and physician may be achieved if a "normal" tracing can be obtained. One

way to accomplish this is to take the electrocardiogram at a time when as many extraneous factors as possible have been eliminated. This can be done by preparing the patient for the electrocardiogram as carefully as for a basal metabolic rate. In this fashion Sears and Manning were able to obtain normal tracings in 78 of 160 healthy air cadets who had had abnormal routine electrocardiograms[28].

If the basal electrocardiogram is still abnormal, we believe, as a result of our studies, that the use of the erect position is the next step. If further T wave flattening or inversion occurs to a marked degree in the same leads which were abnormal in the recumbent tracing, a physiologic basis for the abnormalities is strongly suggested. As an additional aid the patient may be exercised and hyperventilated. If these maneuvers also produce similar changes, the physician has ample evidence to make a diagnosis of innocent T wave inversion. We believe that further measures utilizing drugs are not indicated because effects produced may be extremely complex and nonspecific as is the case with ergotrate and potassium. In addition, dangerous side effects may be encountered, as with ergotrate which was responsible for a death in one study similar to ours (Scherf and Schlachman[25]).

Summary and Conclusions. The response of the ST-T segment of the electrocardiogram to changes in posture was studied in 2 groups of normal subjects. One of these had abnormal recumbent tracings due to ST-T abnormalities. The other had normal recumbent electrocardiograms. The response to the erect position was marked in the first group, the result being a distinct increase in the abnormalities or a return to normal. Approximately 50% of those who had normal recumbent electrocardiograms developed significant T wave flattening or inversion in the erect position. A number of the possible causes for these changes is discussed. None of them is a completely satisfactory explanation of the phenomenon, but the most likely is related to alterations in sympathetic tone.

All physicians interpreting electrocardiograms should be aware of the many physiologic factors which may affect the ST-T portion of the tracing resulting in "nonspecific" T wave abnormalities. Those related to posture are common but by no means the only ones that will be encountered. A practical approach to the problem of "nonspecific" T wave inversion is presented. It is believed that a knowledge of the phenomenon combined with a high index of suspicion and a utilization of the proposed method of study will eliminate many erroneous diagnoses of heart disease based solely on T wave changes.

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SUMMARIO IN INTERLINGUA

Anormalitate de Unda T in Patientes sin Evidente Morbo Cardiac: Le Effecto del Postura

Le responsa del segmento ST-T del electrocardiogramma a alterationes de postura esseva studiate in 2 gruppos de subjectos normal. Un de istos habeva registrationes anormal in position recumbente como resultato de anormalitates de ST-T. In le altere, le electrocardiogramma in position recumbente esseva normal. Le responsa al transition in postura erecte esseva marcate in le prime gruppo. Le responsa consisteva in un distincte augmento del anormalitates o in un retorno a configurationes normal. Approximativemente 50% del subjectos con normal electrocardiogrammas in position recumbente disveloppava significative grados de applattamento o inversion de unda T in postura erecte. Un numero del causas possibile de iste alterationes es discutite. Nulle de illos representa un explication completemente satisfactori del phenomeno. Le plus probabile es relationate a alterationes del tono sympathic.

Omne medico qui si occupa de interpretar electrocardiogrammas deberea esser conscie del facto que il existe multe factores physiologic le quales pote afficer le portion ST-T del registration e causar assi anormalitates "nonspecific" del unda T. Frequentemente ille factores es relationate con le postura, sed isto non vale in omne le casos. Es presentate un tactica practic pro attaccar le problema del inversion "nonspecific" del unda T. Es opinate que le familiaritate con iste phenomenos, combinate con un alte indice de suspicion e le utilisation del proponite methodo de investigation, va eliminar multe erronee diagnoses de morbo cardiac, basate exclusivemente super alterationes del unda T.

A STUDY OF MIGRAINE PHARMACOTHERAPY

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It is generally agreed that the vasoconstrictor agent ergotamine tartrate is the most effective drug for the alleviation of migraine headache attacks. After its introduction by Maier[16], a series of articles attested to its therapeutic value. And yet, a review of much of this literature (Bercel[2], Dalsgaard-Nielson[6], Dannenberg[7], Friedman, Merritt and von Storch[11], Horton, Peters and Blumenthal[12], Kallós and Kallós-Deffner[14], Lennox and von Storch[15], O'Sullivan[18], Tillgren[19]) revealed a number of unresolved methodologic and pharmacologic problems. Three issues that arose out of this review have engaged our attention and led to the work described here.

First, the methodology of many of these studies exhibited certain limitations. Allowance was usually not made in the experimental design for the effects on headache of suggestion, physical and mental repose, enthusiasm of physician, expectation of patient, and for the naturally variable frequency and intensity of migraine attacks. Marcussen and Wolff[17,21] have amply documented the immediate therapeutic value in migraine attacks of suggestion, rest and reassurance. As many as 52% of subjects have reported relief of headache after placebo (Jellinek[13]). To deal with this methodologic issue, it seemed worthwhile to us to apply to an older problem, migraine pharmacotherapy, some of the newer experimental designs of clinical pharmacology.

Secondly, no general agreement about the effectiveness of orally administered ergotamine tartrate seems to have been reached. After parenteral administration of this agent, headache is relieved in roughly 80 to 90% of cases, whereas ergotamine by mouth has been effective in from 45 to 82% of patients studied (Friedman, Merritt and von Storch[11], Lennox and von Storch[15], O'Sullivan[18]). In the cat, only 30% of orally administered ergotamine is absorbed (Burn[4]). Absorption in man is similarly incomplete. Concern about the value of orally administered ergotamine alone has led to the addition of caffeine to it in an attempt to bolster the effectiveness of the preparation as a vasoconstrictor (Cohen and Criep[5], Friedman and Merritt[10]). In short, doubt exists as to whether orally administered ergotamine tartrate in the usual initial dose of 2 mg. is any more effective than placebo. Since the oral route is by far the most convenient and least expensive one, it seemed important to assay the effectiveness of the drug by that route.

Thirdly, the frequency with which ergotamine induces nausea and vomiting has been a major drawback. To meet this problem, other drugs have been combined with ergotamine tartrate in headache preparations in an attempt to mitigate its nauseant and emetic properties. Belladonna alkaloids such as hyoscyamine and atropine have been employed. More recently, cyclizine (1-Diphenyl methyl-4-methyl-piperazine hydrochloride. 1-Benzhydryl-

4 methylpiperazine hydrochloride), an antihistamine used in the treatment of motion sickness, has been combined with ergotamine tartrate and caffeine in an attempt to reduce the nausea and vomiting that sometimes follow the administration of the latter two agents alone. There has been little attempt to compare the antiemetic effects of such drug combinations.

The present study seeks, through newer clinical pharmacologic methods, to answer two questions. 1) Is ergotamine tartrate, by mouth, any more effective in relieving headache than placebo? 2) How does the combination of ergotamine tartrate, caffeine, and cyclizine compare with placebo and with a headache preparation containing belladonna alkaloids as antiemetics in its capacity to induce vomiting?

Methods. A total of 64 patients were studied. In all patients, each of the following diagnostic criteria for migraine was present.

1) A periodic, recurrent headache, unilateral at its onset.

2) A family history of similar headaches.

3) The presence of some gastrointestinal symptoms such as anorexia, nausea, vomiting during the headache attack.

4) Some evidence that extracranial vasodilatation in the area of headache occurred during the attack. A dilated, tender scalp or face artery, bulbar conjunctival injection or a history of relief after parenterally administered vasoconstrictor agents, or both, constituted such evidence.

The 64 patients were a heterogeneous group, reflecting the available supply of subjects. About half the group (31 subjects) consisted of Negro female hospital or clinic patients, one-quarter (18 subjects) of male medical students, female hospital secretaries and technicians, and about one-quarter (15 subjects) of Caucasian private patients, both male and female. In all there were 47 women and 17 men. The age range was 22 to 53, with a mean of 36.2. None of the subjects exhibited major illnesses in addition to migraine. All were informed that they were participating in a trial to select a good headache preparation. All subjects were seen within 55 minutes of the onset of the headache attack. First, a brief examination was carried out to make certain that the headache was migraine. Hereafter the procedure differed depending on the experimental question asked of the particular subject on that occasion. In all instances, except as hereinafter described, both patient and investigator were ignorant of the exact identity of the preparation used until after the results were obtained.

In 44 patients, the effectiveness of orally administered ergotamine tartrate was compared with that of an identical appearing placebo. On the first headache occasion, these subjects ingested either five 1 mg. ergotamine tartrate tablets or five placebo tablets. On the second headache occasion, the alternative preparation was administered. The order of administration of the two preparations was randomly determined.

Immediately before, and at 15-minute intervals after receiving the drug or placebo, the subject estimated the intensity of the headache in arbitrary units. On a scale of 1 to 10, one unit corresponded to barely perceptible head pain, 10 to the most severe headache the subject recalled. Most of the predrug estimates of severity in this study ranged from 5 to 8 units. The post drug period of observation was one hour and 15 minutes. If sometime during this period the patient estimated that the headache was at least 50% relieved and if such relief was maintained for the remainder of the observation period, the result was considered positive. If the estimated headache intensity decreased from 8 to 4 units or 7 to 3 units after treatment, 50% or more of the headache was considered to have been relieved. A decrease in headache intensity from, let us say, 8 to 5 units was not considered significant relief.

In most of the patients, some abnormal physical findings were present during the headache attacks. There were tender dilated extracranial arteries, bulbar conjunctival injection, and well defined areas of scalp and face tenderness. Such findings were recorded, observed at intervals after drug administration, and the effects of the agents on them as well as on headache intensity noted.

The effectiveness of ergotamine as compared to placebo was determined by a sequential analysis design. The plan used was developed by Bross[3]. The following decisions were made about the sequential plan.

1. The probability of type I error, that is, of recommending ergotamine when in fact it is no better than the placebo = .05.

2. The probability of type II error, that is, of failing to recommend ergotamine when,

in fact, it is better than the placebo = .14.

3. Ergotamine tartrate may be expected to alleviate headache in at least 70% of patients.

4. Placebo may be expected to relieve headache in 50% of patients.

Therefore, let P_1 equal the proportion of patients obtaining relief from placebo = 0.5 (50%).

Let P_2 equal the proportion of patients obtaining relief from ergotamine = 0.7 (70%).

Then the likelihood of each of the four following outcomes of the experiments is given as follows:

	Placebo	*Ergotamine*	*Probability of Outcome*
a	relief	relief	$P_1 P_2 = (.5)(.7) = .35$
b	no relief	no relief	$(1-P_1)(1-P_2) = (.5)(.3) = .15$
c	relief	no relief	$P_1(1-P_2) = (.5)(.3) = .15$
d	no relief	relief	$(1-P_1)P_2 = (.5)(.7) = .35$

The proportion P° is defined as:

$$P^\circ = \frac{P_2(1-P_1)}{P_2(1-P_1) + P_1(1-P_2)},$$ that is, the proportion of patients in outcome "d" to the total number of patients in outcomes "c" + "d". Ergotamine is said to be significantly better than placebo if $P^\circ = .70$. In other words, if 50% of patients obtain relief after placebo, we will say that ergotamine is better therapy if it induces relief in 70% of patients. For more details, the reader is referred to Bross[3] and to Wald[20].

This sequential plan is shown in Fig. 1. The plotting of results was carried out as follows. If one patient experienced relief after ergotamine but not after placebo, an X was made in the space above the last entry. If a patient experienced relief after placebo but not after ergotamine, an X was placed in the space to the right of the last entry. Plotting of subjects was continued until one of the boundaries between significance levels was crossed. This occurred after 28 patients

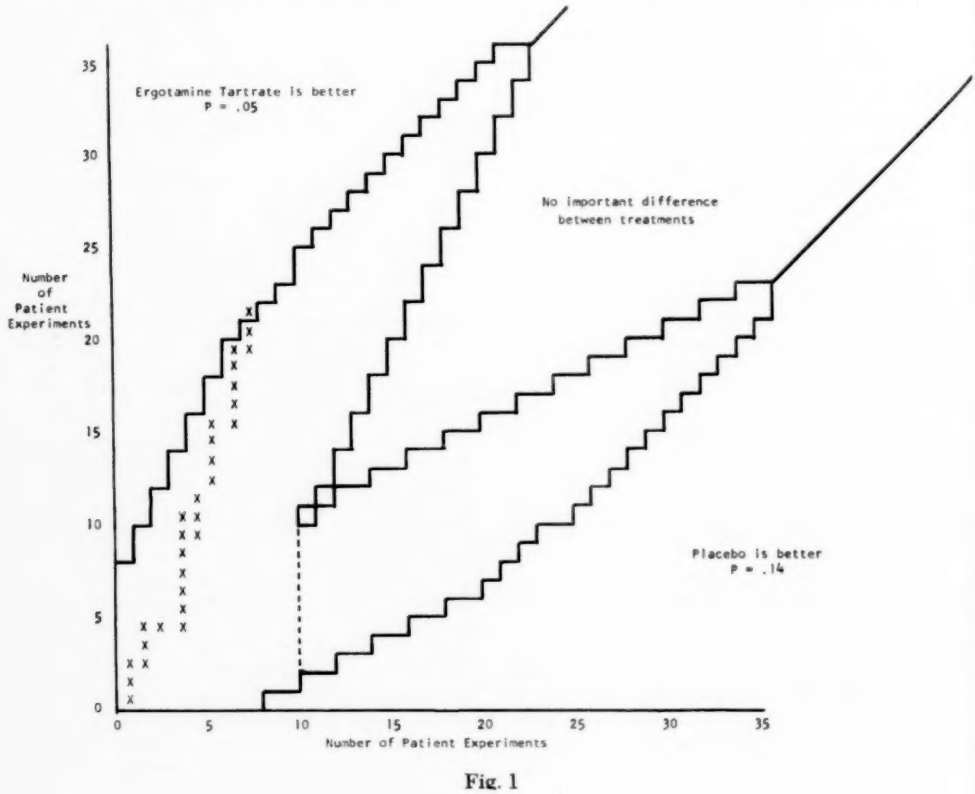

Fig. 1

had been plotted. Patients in whom placebo and drug had the same effect; that is, outcomes "a" and "b", were not included in the analysis. Thus, in accordance with the assumptions and methods of this test, data on 16 patients were not plotted.

A second comparison was made in 19 additional subjects. The emetic effects of the cyclizine-containing headache preparation were compared with those of an identical appearing placebo. On the first headache occasion, these subjects ingested either 5 placebo tablets or 5 drug tablets, each of which contained 1 mg. ergotamine tartrate, 25 mg. cyclizine hydrochloride and 50 mg. caffeine. The alternate preparation was used on the second headache occasion. Order of drug administration was randomly determined. Vomiting occurring sometime between 15 minutes and one hour and 15 minutes after the drug or placebo administration was recorded.

In the third comparison, the incidence of vomiting occurring after one headache preparation (tablets containing 1 mg. ergotamine tartrate, 25 mg. cyclizine hydrochloride, and caffeine 50 mg.) was compared with that occurring after another (tablets containing 1 mg. ergotamine tartrate, 100 mg. caffeine, 0.1 mg. belladonna alkaloids as hyoscyamine sulfate and atropine sulfate, and acetophenetidin 130 mg.). The 43 subjects employed in the third comparison, with a single exception, had participated in one of the other two studies. All but one of those who were invited to participate consented. The invitation to participate depended on the geographic availability of the subject. The third comparison was not double blind. The investigator recognized the preparations by their appearance and the patients were aware that two kinds of tablets were being used. In randomized order, 5 tablets of one preparation were administered on the first headache occasion and 5 tablets of the other during the second attack.

The results of the last two comparisons in terms of vomiting, not vomiting, were tabulated in 2 $\times$2 contingency tables. The number of patients is the unit in these tables. That modification of the chi square test employed by Denton and Beecher[8,9] and discussed by Mosteller[1] was used in the analysis. The method compares only those subjects responding differently to the two treatments.

Results. The results of all trials on all patients who received ergotamine tartrate and placebo are shown in Table 1. There were a total of 88 headache episodes, 44 treated with ergotamine and 44 with placebo. Twenty-one subjects reported 50% or more relief after ergotamine tartrate but not after placebo. Seven were helped by placebo but not ergotamine. Six subjects reported no relief from either agent and 10 experienced relief after both.

TABLE 1

		PLACEBO		
		Relief	*No Relief*	*Total*
ERGOTAMINE TARTRATE	Relief	10	21	31
	No relief	7	6	13
	Total	17	27	44

Figure 1 shows the plots of the 28 patients who responded differently to the two agents employed, that is, placebo and ergotamine tartrate. Note that the line of plotting crossed the barrier from the central squared area into the upper left hand area wherein the results mean that ergotamine is significantly better than placebo. This crossing of the "significance barrier" occurred after a total of 44 patients had received ergotamine on one occasion and placebo on another. When a signifi-

cant difference between ergotamine and placebo was attained, 21 had responded to ergot and not to placebo, and 7 had responded only to placebo.

In all but 4 of the 88 headache episodes observed in these patients, one or more abnormal physical findings were noted during the headache attack. In the 31 headaches that responded favorably to ergotamine, 25 episodes of headache relief were accompanied by a detectable decrease in intensity of one or more of the above mentioned physical signs. In the 17 headaches that responded favorably to placebo, 11 episodes of headache relief were associated with a decrease in intensity of the same signs.

Table 2 shows the comparison in the occurrence of vomiting after placebo and after a total dose of 5 mg. ergotamine tartrate, 250 mg. caffeine and 125 mg. cyclizine hydrochloride (Combination B). Three patients vomited both after drug and after placebo, 2 vomited after placebo but not after drug, 4 vomited after drug but not after placebo and 10 did not vomit on either occasion. $x^2 = .17$. There was no significant difference between the effects of placebo and of this drug combination in inducing vomiting.

Table 3 shows the comparison in incidence of vomiting after the two headache preparations. In Combination A trials, each total dose was 5 mg. ergotamine tartrate, 500 mg. caffeine, .5 mg. levo-rotatary belladonna alkaloids (87.5% hyoscyamine, 12.5% atropine as sulfates) and 650 mg. acetophenetidin. In Combination B trials patients received 5 mg. ergotamine tartrate, 250 mg. caffeine, and 125 mg. cyclizine hydrochloride. Four subjects vomited in both drug trials and 23 in neither. Twelve vomited after Combination A but not after B and 4 vomited after Combination B but not A. $x^2 =$

TABLE 2.—COMPARISON OF OCCURRENCE OF VOMITING AFTER PLACEBO AND AFTER COMBINATION B

		PLACEBO		
		Vomiting	*Not Vomiting*	*Total*
COMBINATION B	Vomiting	3	4	7
	Not vomiting	2	10	12
	Total	5	14	19

TABLE 3.—INCIDENCE OF VOMITING AFTER HEADACHE COMBINATION A AND B

		COMBINATION A		
		Vomiting	*Not Vomiting*	*Total*
COMBINATION B	Vomiting	4	4	8
	Not vomiting	12	23	35
	Total	16	27	43

3.38 P<.10. Combination A induced more vomiting than Combination B but the difference was not quite significant at the commonly accepted probability level of .05. For P to equal .05 x^2 must be 3.84. Because of irrelevant problems connected with the duties of the investigator, it was not possible to increase the number of patient trials, even though a greater number of subjects might have brought about a higher level of significance in the results.

Discussion. The results indicate that in a dose of 5 mg., orally administered ergotamine tartrate was significantly more effective than placebo. The 5-mg. dose is larger than that commonly employed. The usual procedure is to administer 2 mg. ergotamine tartrate by mouth either alone or in combination with other agents, and then 1-mg. increments at roughly one-half to one hour intervals thereafter as needed. In view of the well known fact that ergotamine is much less effective when given late in the headache period, it seems worthwhile to administer a single large dose as close to the onset of headache as possible. The principal reason that larger doses have not been employed is the fear of toxic effects. Of such effects the most common are nausea and vomiting. Since our results indicated that the addition of cyclizine to ergot reduced the frequency of vomiting to a value only slightly greater than that for placebo-treated migraine, concern over this single aspect of ergotamine toxicity seems less warranted.

In comparing the two headache Combinations A and B, the differences in emetic effects cannot be attributed solely to differences in anti-emetic properties of cyclizine and belladonna alkaloids. The dose of caffeine was twice as large in Combination A as in B, and Combination A contained acetophenetidin as well. Differences in the emetic effects may be related to the possible nauseous properties in some patients of acetophenetidin and of larger doses of caffeine.

Summary and Conclusions. 1. Orally administered ergotamine tartrate in a single 5-mg. dose was significantly more effective than placebo in relieving migraine headache in 44 subjects.

2. A single dose of one headache preparation containing 5 mg. ergotamine tartrate, 250 mg. caffeine and 125 mg. cyclizine caused no more vomiting than placebo in another population of 19 subjects.

3. In 43 subjects, a dose of headache Combination A (5 mg. ergotamine tartrate, .5 mg. levo-rotatory belladonna alkaloids, 500 mg. caffeine, and 650 mg. acetophenetidin) induced more vomiting than a dose of Combination B (5 mg. ergotamine tartrate, 250 mg. caffeine and 125 mg. cyclizine).

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SUMMARIO IN INTERLINGUA

Un Studio del Pharmacotherapia de Migraine

1. Tartrato de ergotamina, administrate per via oral in un dose unic de 5 mg, esseva significativemente plus efficace que placebo in le alleviamento de migraine in 44 subjectos.

2. Un sol dose de un preparato pro mal de capite, continente 5 mg de tartrato de ergotamina, 250 mg de caffeina, e 125 mg de cyclizina, non causava plus vomito que un placebo in un altere gruppo de 19 subjectos.

3. In 43 subjectos, un dose de Combination A pro mal de capite (5 mg de tartrato de ergotamina, 0,5 mg de alcaloides de belladonna levo-rotatori, 500 mg de caffeina, e 650 mg de acetophenetidina) induceva plus vomito que un dose de Combination B (5 mg de tartrato de ergotamina, 250 mg de caffeina, e 125 mg de cyclizina).

NIALAMIDE ALONE AND IN COMBINATION WITH THIAZIDE DERIVATIVES IN THE TREATMENT OF ESSENTIAL HYPERTENSION*

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Despite the availability of numerous effective antihypertensive agents, the search continues for additional drugs of equal or greater potency with fewer untoward reactions. At present, a variety of new compounds with differing pharmacodynamic mechanisms of action are being investigated. The monoamine oxidase inhibitors are of particular interest since these agents interfere with the normal degradation of various naturally occurring monoamines including norepinephrine and serotonin. It is the purpose of this report to appraise the effectiveness of nialamide alone and in combination with thiazide derivatives in the treatment of essential hypertension.

Methods and Materials. NIALAMIDE ALONE. Twenty-five ambulatory patients with blood pressures greater than 150/100 were randomly selected from the Hypertension Clinic. After an initial diagnostic evaluation, these subjects were given daily placebo medication for a minimum period of at least 3 weeks. The patients returned to the clinic at weekly intervals, at which time blood pressure and physical signs and symptoms were recorded. After the control period, nialamide† was begun in a dosage of 75 mg. daily (25 mg. t.i.d.); thereafter the dosage was increased at biweekly intervals to a maximum of 225 mg. daily (75 mg. t.i.d.) unless a significant antihypertensive response‡ was achieved at a lower dosage. Treatment with nialamide alone was continued for a minimum period of 8 weeks.

NIALAMIDE PLUS HYDROCHLOROTHIAZIDE. Hydrochlorothiazide was added to the therapeutic regimen in 17 subjects from the previous group in whom a significant hypotensive response had not been achieved. The initial dosage of hydrochlorothiazide§ was 50 mg. daily (25 mg. b.i.d.). After 2 weeks, the dosage was increased to 100 mg. per

*This investigation was supported in part by research grants from National Institutes of Health, U.S. Public Health Service (H-3550-C) and Chas. Pfizer Co., Inc.

†Supplied as Niamid by Chas. Pfizer Co., Inc., New York, New York.

‡A reduction in mean arterial blood pressure (diastolic pressure plus 1/3 of the pulse pressure) of 20 mm. Hg or more was considered significant.

§Supplied as Hydrodiuril by Merck, Sharp & Dohme, West Point, Pennsylvania.

TABLE 1.—BLOOD PRESSURE RESPONSE TO NIALAMIDE WHEN GIVEN ALONE AND IN COMBINATION WITH THIAZIDE DERIVATIVES

Drug	*No. of Patients*	*Supine*			*Erect*		
		*Normotensive**	*Mean Blood Pressure Reduced >20 mm. Hg or Normotensive*	*Unresponsive*	*Normotensive**	*Mean Blood Pressure Reduced >20 mm. Hg or Normotensive*	*Unresponsive*
Nialamide	25	5	5	20	7	11	14
Nialamide plus Hydrochlorothiazide	17	3	3	14	7	11	6
Nialamide plus 3-Benzylthiomethylchlorothiazide	22	6	13	9	13	16	6

*Blood pressure reduced to 150/90 mm. Hg or less

day (50 mg. b.i.d.) if a significant blood pressure reduction had not been obtained. The combination of nialamide (75 mg. t.i.d.) and hydrochlorothiazide was administered for a minimum period of 8 weeks.

NIALAMIDE PLUS 3-BENZYLTHIOMETHYLCHLOROTHIAZIDE. Twenty-two additional patients with control pressures greater than 150/100 were treated with the combination of nialamide and 3-benzylthiomethylchlorothiazide.* Nialamide was begun in a dosage of 225 mg. per day (75 mg. t.i.d.), and the initial dosage of 3-benzylthiomethylchlorothiazide was 100 mg. daily (50 mg. b.i.d.). After 2 weeks, the dosage of the latter drug was increased to 200 mg. per day (100 b.i.d.) in those patients in whom a significant antihypertensive response had not been obtained. The combination of nialamide and 3-benzylthiomethylchlorothiazide was administered for a minimum interval of 8 weeks.

Results. NIALAMIDE ALONE. The blood pressure response is tabulated in Table 1. Of the 25 patients in this group, 5 (20%) obtained a drop in mean arterial pressure of more than 20 mm. mercury in the supine position. When blood pressure was measured in the erect position, 11 patients (44%) obtained a significant hypotensive response and 7 of the 11 became normotensive.

The side reactions and beneficial effects are listed in Tables 2 and 3 respectively. No serious reactions were encountered. Drowsiness, orthostatic weakness, dreams, and anxiety were the most prominent complaints but were seen in only a few patients.

NIALAMIDE PLUS HYDROCHLOROTHIAZIDE. The blood pressure response is tabulated in Table 1. Among the 17 patients who received combined therapy with nialamide and hydrochlorothiazide, only 3 (18%) obtained a reduction in mean arterial blood pressure of more than 20 mm. mercury in the supine position. However, when the blood pressure was recorded in the upright position, 11 subjects (65%) obtained a significant hypotensive response and 7 of the 11 became normotensive (see Fig. 1).

TABLE 2.—SIDE EFFECTS EXPRESSED IN PER CENT OF PATIENTS TREATED

Side Effect	*Nialamide alone*	*Nialamide plus Hydrochlorothiazide*	*Nialamide plus 3-Benzylthiomethyl-chlorothiazide*
Headache	8	6	5
Dry Mouth	8	—	14
Nasal Congestion	8	6	14
Edema	8	6	5
Increased Appetite	12	12	5
Nausea	4	6	5
Constipation	8	24	5
Orthostatic Weakness	25	24	27
Drowsiness	28	41	23
Depression	8	12	9
Dreams	20	24	5
Anxiety	20	6	9

The side effects and beneficial effects are tabulated in Tables 2 and 3 respectively. The most common side reaction was drowsiness which occurred in 7 patients. Less common complaints were orthostatic weakness, constipation and dreams.

NIALAMIDE PLUS 3-BENZYLTHIOMETHYLCHLOROTHIAZIDE. The blood pressure response is tabulated in Table 1. Of the 22 patients in this group, 13 (59%) obtained a drop in mean pressure of 20 mm. mercury or more

*Supplied as Urese by Chas. Pfizer Co., Inc., New York, New York.

TABLE 3.—BENEFICIAL EFFECTS EXPRESSED IN PER CENT OF PATIENTS IMPROVED

	Nialamide alone		*Nialamide plus Hydrochlorothiazide*		*Nialamide plus 3-Benzylthiomethylchlorothiazide*	
Symptom	*No. of Patients Who Complained Before Therapy*	*% Improved*	*No. of Patients Who Complained Before Therapy*	*% Improved*	*No. of Patients Who Complained Before Therapy*	*% Improved*
Headache	9	33	6	67	11	64
Chest Pain	—	—	—	—	1	100
Dyspnea	6	50	5	40	7	29
Edema	2	50	1	100	2	50
Nausea	1	100	1	100	2	50
Constipation	2	50	1	100	6	50
Dizziness	10	30	8	38	10	30
Depression	1	100	1	100	4	50
Anxiety	3	67	2	50	5	60

in the supine position. In the erect position, 16 subjects (73%) achieved a significant blood pressure reduction and 13 of the 16 became normotensive (see Fig. 2).

The side reactions and beneficial effects are recorded in Tables 2 and 3. As with the previous two groups, the most prominent side effects were orthostatic weakness and drowsiness.

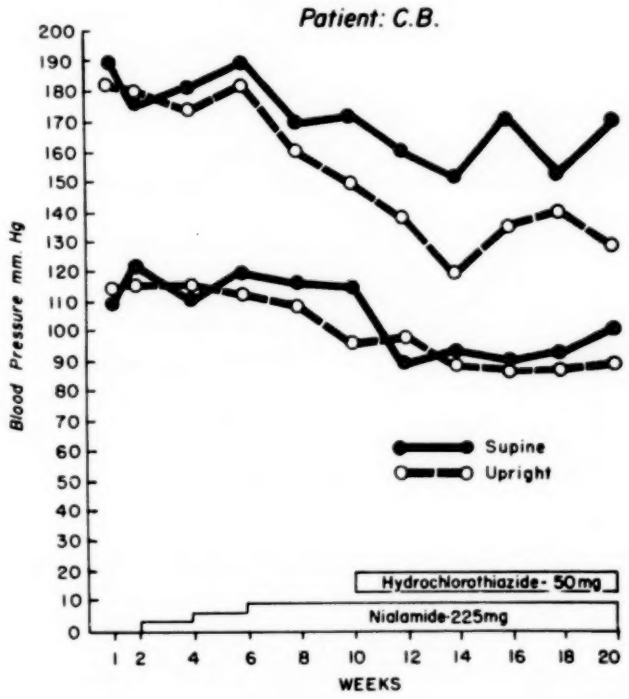

Fig. 1.—A significant orthostatic antihypertensive response was accomplished with nialamide and hydrochlorothiazide.

Discussion. Despite extensive biochemical and pharmacodynamic investigations, the mechanism of antihypertensive action of the monoamine oxidase inhibitors has not been precisely defined. Monoamine oxidase (MAO) is an enzyme which actively destroys various monoamines including norepinephrine, epinephrine, and serotonin. It would, therefore, be anticipated that the MAO inhibitors would cause an accumulation of these hormones in nerve and muscle tissues where they normally account for neurogenic transmission and smooth muscle contraction. Consequently it seems rather paradoxical that hypotension should occur since the expected result would be a hypertensive response secondary to the increased concentration of these various pressor substances.

It now appears, however, that the principal pathway for the metabolism of epinephrine and norepinephrine is probably O-methylation to metanephrine, a physiologically inactive metabolite (Axelrod[1]). This biochemical process is catalyzed by the enzyme, catechol-o-methyl transferase. The latter enzyme most likely plays a greater role

in the deactivation of epinephrine and norepinephrine than does monoamine oxidase.

The MAO inhibitors actually possess a number of separate actions which could conceivably account for their hypotensive abilities. Animal studies accompanied by significant parasympatholytic side reactions (Finnerty and Massaro[5], Gillespie, Terry and Sjoerdsma[7]). The latter effect, therefore, suggests that the ganglioplegic and hypotensive actions of these drugs may not be related.

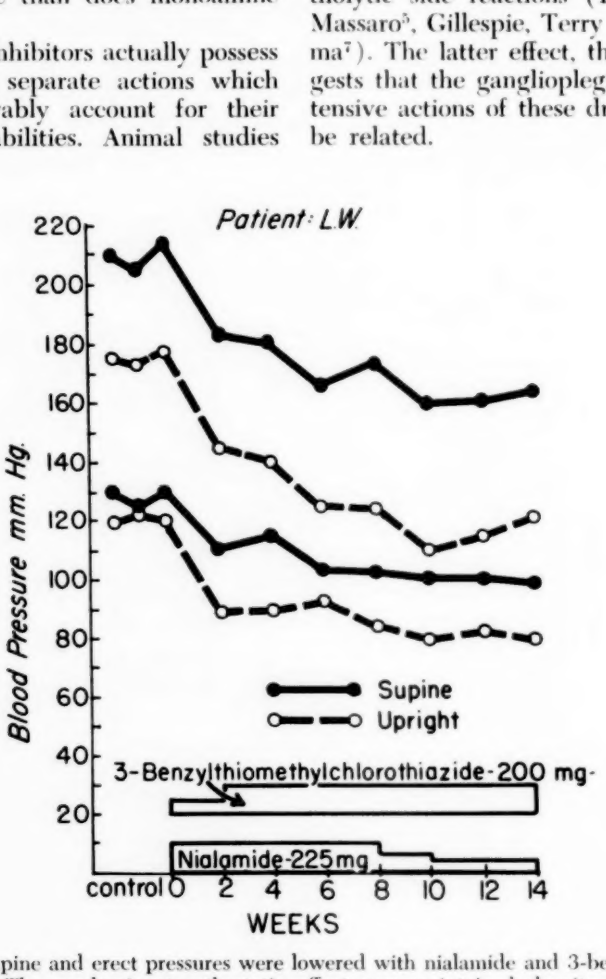

Fig. 2.—Both supine and erect pressures were lowered with nialamide and 3-benzylthiomethylchlorothiazide. The predominant orthostatic effect was maintained despite the subsequent reduction in nialamide dosage.

indicate that several compounds, including iproniazid and JB-516, block neurogenic transmission within the autonomic ganglia (Gertner[6]). In addition, the side effects encountered clinically with iproniazid are similar to those obtained with the classical ganglionic blocking agents. However the clinical use of other inhibitors, including nialamide and JB-516, has not been

It has also been postulated that the antihypertensive action of the MAO inhibitors might reflect their adrenergic blocking activities (Balzer and Holtz[3], Kamijo, Koelle and Wagner[9], Zeller[13]). However there is no apparent correlation between hypotensive effect observed clinically and adrenergic blocking action as measured on isolated seminal vesicles *in vitro* (Zbinden,

Randall and Moe[12]). Therefore it appears that this latter pharmacologic attribute is probably not a very important factor in the hypotensive action of these drugs.

In addition to their effect on monoamine oxidase activity, iproniazid and various of its analogues also inhibit several other enzyme systems. These include guanidine deaminase, 5-HTP decarboxylase, some diamine oxidase, succinic dehydrogenase, and others (Zeller *et al.*[14]). The hypotensive abilities of the MAO inhibitors may be related, at least in part, to these additional enzymatic activities. Further investigative study of these mechanisms is indicated.

MAO inhibition increases the concentration of various biological amines within the body tissues (Pletscher and Pellmont[10], Udenfriend, Weissbach and Bogdanski[11]). This latter action may be the most important of all since certain investigations suggest that the accumulation of catecholamines due to MAO inhibition decreases the norepinephrine sensitivity of the tissues and thereby protects the cells against exogenous catecholamines. For example, Bachtold and Pletscher have shown that norepinephrine-induced contraction of the isolated rabbit aorta is significantly reduced after pretreatment with iproniazid[2]. This reduced norepinephrine sensitivity could conceivably explain the antihypertensive effect of the MAO inhibitors.

Finally, Brodie has postulated that norepinephrine and serotonin act as neuro-hormones within the central nervous system to control and regulate various autonomic, somatic, and psychogenic functions[4]. Since the use of the MAO inhibitors results in an increased concentration of these substances within the brain substance, it is conceivable that the hypotensive abilities of these compounds may also be related to this particular effect.

It is apparent that the exact hypotensive mechanism of action of the MAO inhibitors still remains undetermined. Yet the hypotensive abilities of the MAO inhibitors is indisputable. Iproniazid, JB-516, and nialamide have all demonstrated significant antihypertensive abilities (Finnerty and Massaro[5], Gillespie, Terry and Sjoerdsma[7], Hollander and Wilkins[8]). In addition, it has been shown that their effectiveness is potentiated by the therapeutic addition of the thiazide derivatives.

The present study confirms the antihypertensive action of nialamide used alone and in combination with hydrochlorothiazide and 3-benzylthiomethylchlorothiazide. Nialamide alone produced only a modest antihypertensive effect. However the therapeutic combination with thiazide derivatives provided a very effective therapeutic regimen for patients with moderate diastolic blood pressure elevation.

Further study of the clinical usefulness of the MAO inhibitors in essential hypertension is warranted. Because of the additional beneficial effects of these compounds in the treatment of angina pectoris and mental depression, it may well be that these drugs will be particularly indicated in the hypertensive patient with complicating coronary artery disease or the depressed patient with diastolic blood pressure elevation.

Summary. Nialamide administered alone in relatively high dosage (225 mg. daily) produced a significant orthostatic antihypertensive effect in 11 of 25 patients. When used in combination with hydrochlorothiazide or 3-benzylthiomethylchlorothiazide, the hypotensive effect was significantly potentiated. Eleven (65%) of 17 treated with nialamide and hydrochlorothia-

zide had a significant response in the erect position, and 16 (73%) of 22 were responsive to nialamide plus 3-benzylthiomethylchlorothiazide.

The mechanism of antihypertensive action of the monoamine oxidase inhibitors remains obscure. Various speculative mechanisms are discussed.

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SUMMARIO IN INTERLINGUA

Nialamida, Sol e in Combination con Derivatos de Thiazida, in le Tractamento de Hypertension Essential

Le administration de relativemente alte doses de nialamida sol (225 mg per die) produceva un significative effecto antihypertensive orthostatic in 11 de 25 patientes. Quando le droga esseva usate in combination con hydrochlorothiazida a 3-benzylthiomethylchlorothiazida, le effecto hypotensive esseva potentiate significativemente. Dece-un de 17 patientes tractate con nialamida e hydrochlorothiazida (65%) manifestava un responsa significative in le position erecte, e 16 de 22 patientes (73%) respondeva similemente a nialamida in combination con 3-benzylthiomethylchlorothiazida.

Le mechanismo del action antihypertensive de inhibitores de oxydase de monoamina remane obscur. Varie speculationes relative a iste question es discutite.

SERIAL FIBRINOGEN DETERMINATIONS IN PATIENTS WITH LEUKEMIA*

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Alterations in the plasma fibrinogen concentration in a variety of diseases are thought to mirror tissue damage and to indicate changes in the degree of activity of the underlying disease processes (Fletcher, Dauphinee and Ogryzlo[3], Foster and Whipple[4], Ham and Curtis[10], Hidalgo, Fowell and Ralls[12], Losner and Volk[16], Losner, Volk and Wilensky[17], McLester, Davidson and Frazier[18]). The significance of fluctuations in fibrinogen in patients with leukemia is less clearly understood. Studies reporting fibrinogen values in leukemia have usually been more concerned with bleeding episodes or changes in other blood proteins (Cooperberg and Neiman[1], Freeman[5], Freeman and Buckley[6], Freeman and Hyde[7], Giraud *et al.*[8], Hillestad[13], Lewis *et al.*[15], Petermann, Karnofsky and Hogness[20], Pisciotta and Schulz[21]). The purpose of the present study is to correlate fluctuations in the plasma fibrinogen values with clinical complications recognized during the course of leukemia.

Material and Methods. Fibrinogen concentrations were measured turbidimetrically using Parfentjev's reagent[19]. Based on single measurements in our laboratory obtained from 68 healthy individuals, fibrinogen values outside of the range of 115 to 400 mg. per 100 ml. were considered abnormal. If the fibrinogen concentration was below 115 mg. per 100 ml. the whole blood clot was observed for *in vitro* lysis (Ham[9]). The study group was composed of 26 patients, 5 with blastic, 9 with chronic granulocytic, and 12 with chronic lymphocytic leukemia. There were 9 females and 17 males whose ages ranged from 14 to 79 years. Appropriate laboratory studies were performed on each patient as prompted by their clinical status. The total period of observation for all of the patients was 2,256 days, during which time 225 fibrinogen values were obtained. Fibrinogen determinations were made from one to 3 times a week if the patient was hospitalized or on each visit if seen in the clinic. The frequency of fibrinogen determinations varied with the activity of the disease and did not adhere to a predetermined schedule. When one or more consecutive fibrinogen value was abnormal,

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that entire period of the patient's illness was scrutinized in an attempt to identify some complicating event. It is this analysis which will be presented.

Results. 1. HEALTHY SUBJECTS. The mean plasma fibrinogen value for the 68 healthy subjects was 258 mg. per 100 ml. The range for 2 standard deviations about the mean was 117 to 339 mg. per 100 ml. These values are similar to those reported by others (Parfentjev, Johnson and Cliffton[19]).

2. LEUKEMIC PATIENTS. Peripheral blood values and bone marrow differentials are not tabulated since they appeared to show no relationship to fluctuations in fibrinogen values. As shown in Table 1, more than half of the 225 fibrinogen determinations were abnormal, 108 being elevated and 9 decreased. Since the fibrinogen response differed with the type of leukemia, the data from the patients with blastic, chronic granulocytic, and chronic lymphocytic leukemia will be considered separately.

a. *Blastic Leukemia.* There were 3 patients with blastic lymphocytic and 2 with blastic granulocytic leukemia. There were 49 elevated fibrinogen determinations seen in this group (Table 1). These fell into 12 periods, and all 5 of the patients had one or more of these episodes of hyperfibrinogenemia. The majority of these were associated

TABLE 1.—COMPOSITION OF THE STUDY GROUP

	Blastic Leukemia	*Chronic Granulocytic Leukemia*	*Chronic Lymphocytic Leukemia*
Number of patients	5	9	12
Total days of observation	451	571	1234
Number of fibrinogen determinations	76	50	99
Number above 400 mg./100 ml.	49	31	28
Number from 115 to 400 mg./100 ml.	23	19	66
Number below 115 mg./100 ml.	4	0	5

TABLE 2.—RECOGNIZABLE CONDITIONS ASSOCIATED WITH HYPERFIBRINOGENEMIA

Type of Leukemia	*Hyperfibrinogen Periods*	*Associated Conditions*			
		Infection	*Infection and Bleeding*	*Other*	*Unknown*
Blastic (5 pts.)	12	2	7	1*	3
Chronic Granulocytic (9 pts.)	18	10	1	2	5
Chronic Lymphatic (12 pts.)	10	5	1	1	3
Total	40	17	9	4	11

*This patient also had infection and bleeding at this time, so that one period of hyperfibrinogen appears twice in the table.

with either infection or infection and bleeding (Table 2). Three of the episodes of hyperfibrinogenemia could not be correlated with a complicating event. However, in 2 of these the patients had been hospitalized in the blastic phase of their disease and the fibrinogen decreased to normal with institution of antileukemic therapy. Five periods of hyperfibrinogenemia were noted at times when the patients were on corticosteroids. Hypofibrinogenemia was noted in one patient who had blastic lymphocytic leukemia. No *in vitro* fibrinolysis was demonstrated, although this patient did have thrombocytopenia and bleeding. On massive doses of hydrocortisone, the platelet

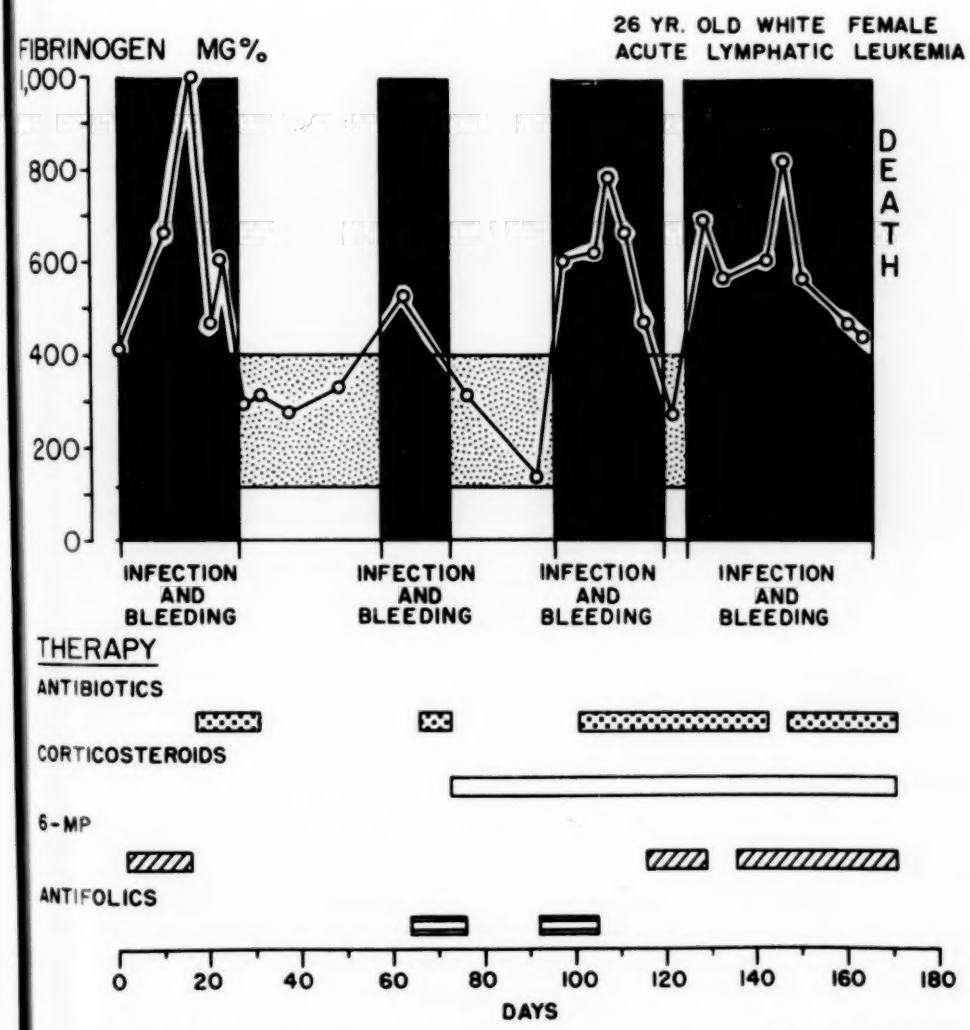

Fig. 1.—Serial plasma fibrinogen concentration in a patient with acute lymphatic leukemia. The 4 periods of hyperfibrinogenemia are shown by the black areas. The stippled area in all figures represents the range of normal plasma fibrinogen.

count returned slowly to normal and the bleeding stopped in spite of continued low fibrinogen values.

Illustrative of this group are the data for one patient which are presented in Fig. 1. Four episodes of hyperfibrinogenemia were noted, each of which was associated with infection and bleeding. There was a temporal relationship between the return of the fibrinogen level to a normal range and clinical improvement following the administration of antibiotics in the first 3 episodes. The fibrinogen was still elevated 11 days prior to her death, at which time her response to antimicrobial therapy was poor. Although corticosteroid therapy was continuous from the 73rd day until her demise, this did not prevent the development of 2 periods of hyperfibrinogenemia.

b. *Chronic Granulocytic Leukemia.* In this group there were 31 elevated fibrinogen values within 18 periods, as

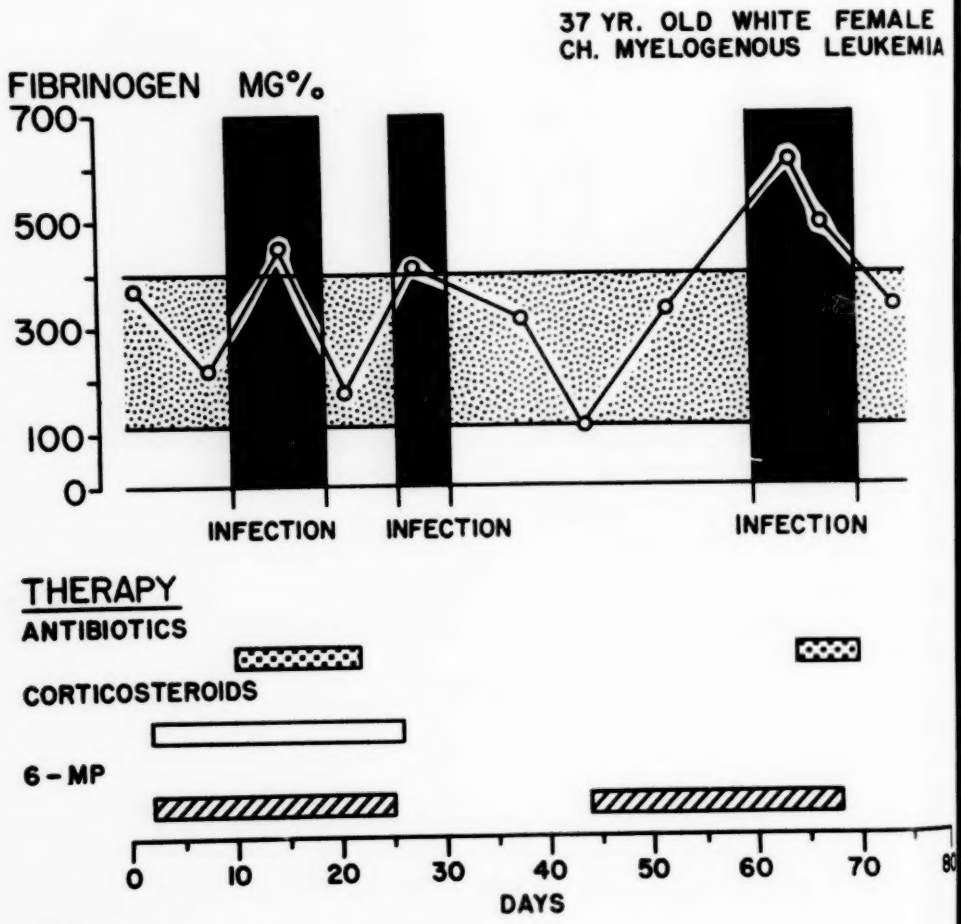

FIGURE 2

Fig. 2.—Serial plasma fibrinogen concentrations in a patient with chronic myelogenous leukemia who had 3 episodes of hyperfibrinogenemia associated with overt infection.

shown in Tables 1 and 2. There were no values below our accepted normal range. Each of the patients exhibited elevated fibrinogens on at least one occasion. Infection was recognized as the complication during 11 of the periods of hyperfibrinogenemia. In 5 instances no specific complication was identified. As for the remaining 2 periods, one was associated with surgery and one with the passage of a renal stone. Three of the periods of abnormal elevations occurred while the patients had infections and were receiving corticosteroids. One patient had a normal fibrinogen value during a proven episode of bacteremia.

Figure 2 presents the fibrinogen values for one patient with chronic granulocytic leukemia. There were 3 periods of hyperfibrinogenemia, each of which was associated with infection. The first occurred during corticosteroid therapy. Two of the infections were treated with antimicrobial agents with general improvement in the patient's condition and a concomitant fall in the fibrinogen level.

c. *Chronic Lymphocytic Leukemia.* In this group, only five of the 12 patients demonstrated high fibrinogen concentrations. These totaled 28 individual determinations and fell into 10 separate periods of observation. Half of these periods were associated with infections (Tables 1 and 2) and 3 occurred during corticosteroid therapy. One elevation appeared at a time when the patient had a pulmonary infarction. The cause of the hyperfibrinogen was not determined in 3 instances. Two patients exhibited hypofibrinogenemia which occurred during periods free of bleeding and of evidence of increased fibrinolytic activity. Later, both patients had normal fibrinogen values. It is interesting that normal fibrinogen concentrations were obtained in one patient during an acute bout of superficial cellulitis.

Figure 3 shows the marked fluctuations in the fibrinogen concentrations seen in one man with chronic lymphocytic leukemia. The patient had been receiving corticosteroids for an autoimmune hemolytic anemia which developed prior to our period of observation. He was admitted with pneumonia and his first plasma fibrinogen was 1,548 mg. per 100 ml. Corticosteroids were continued and he was placed on antimicrobial agents. There was clearing of the pneumonia which was accompanied temporally by a decrease in the fibrinogen. From the 97th to the 104th day of observation, the fibrinogen ranged from 96 to 86 mg. per 100 ml., but there was no evidence of bleeding or *in vitro* clot lysis. The next period of hyperfibrinogenemia was also associated with pneumonia. The patient was still receiving corticosteroids. The cause of the third elevation was not determined. On the 173rd day high values for fibrinogen were again noted. At that time he had developed an infection associated with severe bleeding.

Discussion. Alterations in the plasma fibrinogen occurred irrespective of the stage of leukemia and were not correlated with the total leukocyte count (Ham and Curtis[10], Pisciotta and Schulz[21]). Seventeen of the 40 periods characterized by hyperfibrinogenemia were associated with an infection and 9 more appeared during bouts of infection and bleeding. These 2 complications were seen most frequently in patients with acute leukemia. Others have commented upon the appearance of high fibrinogen values associated with bleeding in patients with acute leukemia (Freeman and Hyde[7]). It has been proposed that the elevation may reflect an impaired conversion of fibrinogen to fibrin resulting from deficiencies in the clotting mechanism secondary to the bleeding. The tissue injury resulting from the frequently asso-

ciated infection, as seen in the present study and reported by others (Freeman[5], Freeman and Buckley[6]), would seem to be an equally tenable explanation. In spite of this apparent correlation between infection and hyperfibrinogenemia, not all patients with an infection respond in this fashion (Hardwicke and Squire[11], Losner and Volk[16], Petermann, Karnofsky and Hogness[20]). Two of our patients illustrated this point, since one with a superficial cellulitis and another with bacteremia had normal fibrinogen concentrations.

Hyperfibrinogenemia was associated with other forms of tissue injury in 4 instances; whereas no complication was recognized in 11. No consistent correlation was noted between either radiation (Foster and Whipple[4]) or anti-

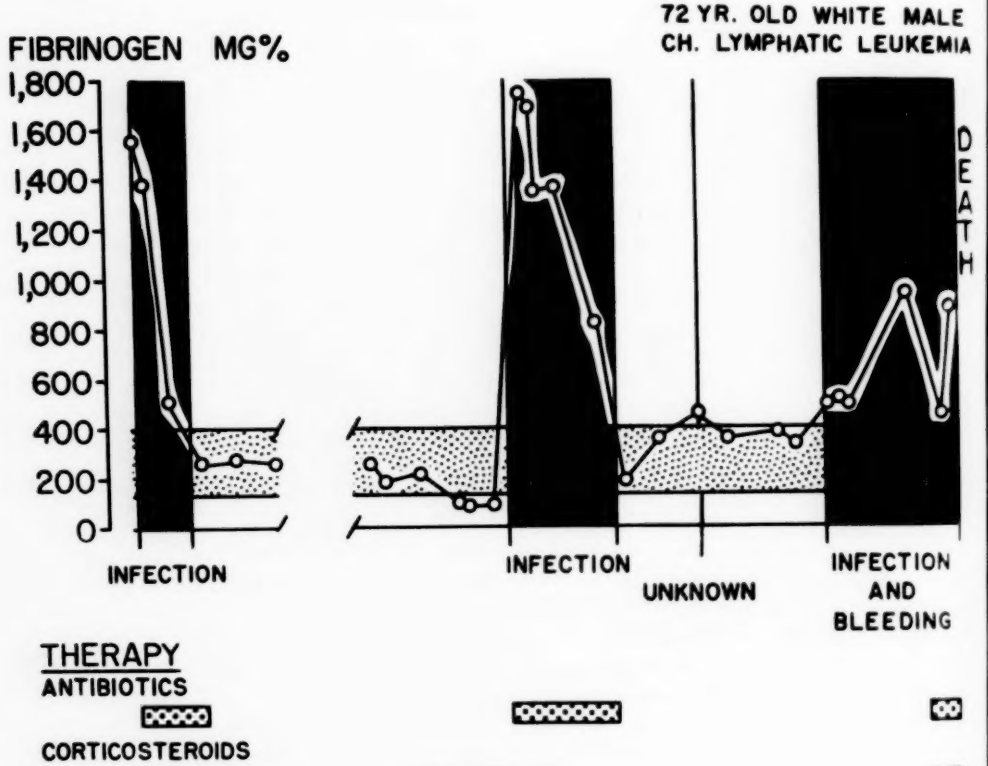

Fig. 3.—Serial plasma fibrinogen concentrations in a patient with chronic lymphatic leukemia. There were 4 episodes of hyperfibrinogenemia. Hypofibrinogenemia was present just prior to the second period of fibrinogen elevation.

metabolite therapy and the fluctuations in plasma fibrinogen content. Normal rats have shown elevated fibrinogen values following aminopterin administration (Rohatgi and Banerjee[22]).

The fibrinogen concentration had some prognostic significance. Of the 8 patients in this series who died while in the hospital, 7 had elevated fibrinogen values from one to 11 days prior to their deaths. All 7 of these patients had infections which were resistant to antimicrobial therapy. The one patient who had a normal fibrinogen determination 5 days before death expired unexpectedly of a myocardial infarction without evidence of infection.

The influence of ACTH and the corticosteroids on the synthesis of fibrinogen has been debated (Fearnley and Bunim[2], Fletcher, Dauphinee and Ogryzlo[3], Kanof, Losner and Volk[14], Vaughan, Bayles and Favour[23]). The fact that these agents may obscure the signs of a complicating infection is well recognized. It is important to emphasize that 9 of the 40 periods of hyperfibrinogenemia occurred in individuals who were receiving corticosteroids. In 8 of these instances a complicating infection was ultimately documented. In this series the administration of corticosteroids did not prevent the increased formation of fibrinogen in response to the tissue damage associated with infection.

Three patients had hypofibrinogenemia. They did not exhibit bleeding or *in vitro* clot lysis. The significance of these low values is not clear. Each patient later demonstrated normal or elevated concentrations. Our experience, and that of others, would seem to support the concept that hypofibrinogenemia *per se* is an infrequent cause of bleeding in leukemia (Cooperberg and Neiman[1], Freeman and Hyde[7], Lewis *et al.*[15], Pisciotta and Schulz[21]). If a fibrinolysin is associated with the low fibrinogen content, however, bleeding is likely to occur (Cooperberg and Neiman[1], Giraud *et al.*[8], Hillestad[13], Pisciotta and Schulz[21]).

Seven of the 26 patients manifested no abnormal fibrinogen values, and all of these had chronic lymphatic leukemia. Our series was too small to evaluate adequately the significance of this.

Summary. 1. Twenty-six patients with leukemia were followed during a portion of their illness and serial fibrinogen concentrations were measured. Over half of the 225 fibrinogen determinations were abnormal. Seven patients, all with chronic lymphatic leukemia, never manifested an abnormal plasma fibrinogen value.

2. Considering single or consecutive values which were elevated as a period of hyperfibrinogenemia, then over half of such periods were either associated with infection alone or with infection and bleeding. In 8 patients, the administration of adrenocorticosteroids at the time that the patient had an infection did not prevent the development of hyperfibrinogenemia.

3. Of the 3 documented episodes of hypofibrinogenemia, none was associated with *in vitro* clot lysis nor could any be directly related to bleeding.

4. A continued elevation of the fibrinogen concentration in the patient with leukemia and an infection indicates a poor response of the infection to therapy and a bad prognosis for the patient.

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SUMMARIO IN INTERLINGUA

Determinationes Serial de Fibrinogeno in Patientes con Leucemia

1. Vinti-sex patients con leucemia esseva tenite sub observation durante un portion de lor morbo, e le concentrationes de fibrinogeno in illes esseva mesurate serialmente. Plus que un medietate del 225 determinationes de fibrinogeno esseva anormal. Tamen, septe patientes—omnes con chronic leucemia lymphatic—nunquam manifestava un valor anormal pro le fibrinogeno de lor plasma.

2. Si nos considera elevationes de valores solitari o consecutive como indication de un periodo de hyperfibrinogenemia, il resulta que plus que un medietate de tal periodos esseva associate con (1) infection sol o (2) infection e sanguination. In 8 patientes, le administration de adrenocorticosteroides al tempore quando le patiente habeva un infection non preveniva le disveloppamento de hyperfibrinogenemia.

3. Tres episodios de hypofibrinogenemia esseva documentate, e nulle de istos esseva associate con lyse de coagulo in vitro, e nulle de illos poteva esser relationate directemente con sanguination.

4. Un continue elevation del concentration de fibrinogeno in patientes con leucemia e un infection reflecte un mal responsa del infection al mesuras therapeutic e suggere un mal prognose pro le patiente.

HEREDITARY PERSISTENCE OF FETAL HEMOGLOBIN

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In a recent survey of the hemoglobin patterns of 1000 consecutive Negro patients admitted to this hospital, a 30-year-old man was discovered with an unexplained level of fetal hemoglobin of over 20% (Myerson, Harrison and Lohmuller[6]). Study of this patient's family has disclosed 2 additional members with a similar pattern. None of the 3 has any apparent difficulties resulting in, or secondary to, the fetal hemoglobinemia.

Case Reports. L.C., a 30-year-old Negro was admitted to the Veterans Administration Hospital, Philadelphia, Pennsylvania, on September 9, 1957, because of abdominal pain. He had been well until 1954, at which time he was hospitalized at another institution because of right upper quadrant abdominal pain associated with fever and jaundice. At exploratory laparotomy a calculous gallbladder was found and removed. Following the operation, the patient had persistent pain in the region of the incision. The pain was nonspecific, unrelated to meals or any other known factors and unaccompanied by other gastrointestinal symptomatology. Review of the patient's past history was negative except for the cholecystectomy. His family history was unremarkable. His father had been killed in an accident at the age of 34. His mother, 4 siblings and 2 children were living and apparently well.

Physical examination revealed a very well developed and nourished Negro who did not appear ill. The entire examination was within normal limits except for the presence of a well healed right upper quadrant abdominal scar which was tender to palpation.

Laboratory studies revealed a hemoglobin of 14 gm. per 100 ml., hematocrit of 47 vol.% and a red blood cell count of 4.89 million per c.mm. The mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, white blood count and differential and platelet count were within normal limits. Serum total protein and albumin globulin ratio, urinalysis, blood urea nitrogen, fasting blood sugar, prothrombin time, serum bilirubin, alkaline phosphatase, blood cholesterol, serum lipase, cephalin flocculation, thymol turbidity and flocculation and retention of bromsulphalein were all within normal limits. A Coombs test was negative in both indirect and direct phases. Red blood cell fragility was normal. The reticulocyte count was 0.4%.

Roentgenograms of the chest and skull, intravenous cholangiography, upper gastrointestinal roentgenogram and intravenous urogram were within normal limits. A routine hemoglobin identification study revealed 22% fetal hemoglobin. The rest of his hemoglobin was A type. A_2 hemoglobin was within normal limits. Between 20 and 25% F hemoglobin was present on repeated occasions at this and other laboratories.

Because of the history of cholelithiasis at the age of 27, records of the patient's previous hospitalization were carefully perused for evidence of hemolysis. None was found and all studies for hemolysis were negative at this hospital. No stigmata of thalassemia were present and the level of A_2 hemoglobin was within normal limits.

Hemoglobin identification was performed on the patient's mother, 2 children and 4 siblings. Two adult sisters had similar findings of increased F hemoglobin, one measuring 18.8% and 22% on 2 occasions, and the other had 21.4% F hemoglobin. The remainder

of the hemoglobin was A in both sisters and there was a normal content of A_2 hemoglobin in both. The patient's mother, his other 2 siblings, as well as his own 2 children had normal hemoglobin patterns. Three children of one of the sisters with fetal hemoglobinemia were studied and found to have normal patterns (Fig. 1). Neither of the 2 affected siblings had any apparent abnormalities to account for the elevation of hemoglobin F and both were in apparent good health.

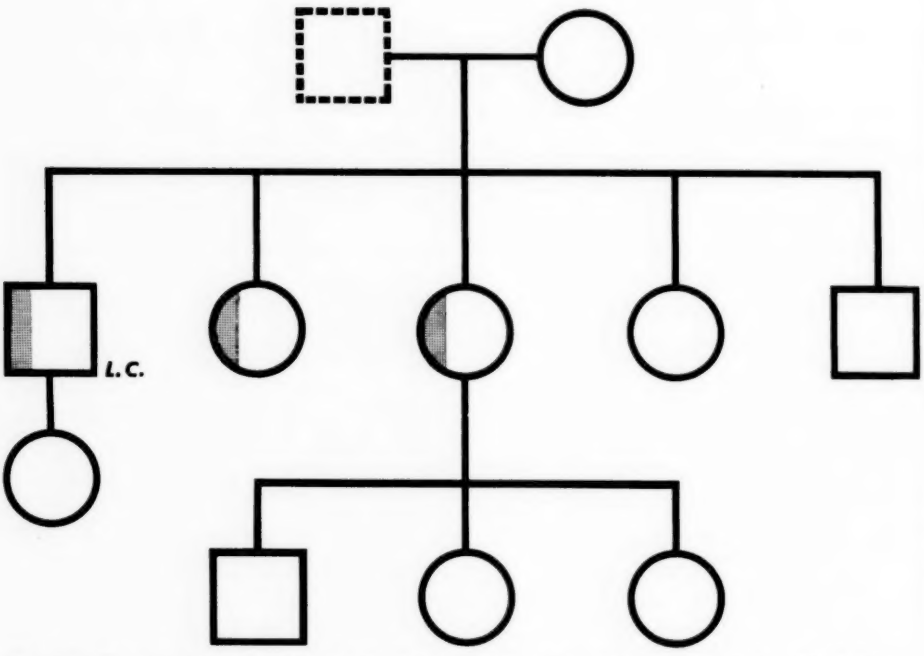

Fig. 1.—Chart showing familial distribution of persistent fetal hemoglobinemia. Shaded compartments indicate affected members. Blank compartments indicate less than 1% hemoglobin.

The patient was restudied in March, 1960, at which time the findings were essentially the same as those on his previous hospitalization. The level of F hemoglobin remains elevated between 20 and 25%.

Discussion. In a study of a group of African subjects with sickle trait thalassemia, Jacobs and Raper found 2 asymptomatic individuals with unaccountable elevations of hemoglobin F and suggested the possibility that hemoglobin F may persist into adult life as a genetic entity without associated hematological abnormality[1].

Went and MacIver described 3 generations of a Jamaican family of African extraction in which several apparently healthy members possessed 16 to 26% F hemoglobin in association with hemoglobin A. Several other members of the family had similar elevations of F hemoglobin associated with an underlying AS pattern[7].

Edington and Lehmann have reported a similar condition in Africa in which the index case was an apparently healthy man with an electrophoretic pattern indistinguishable from sickle cell anemia and with 26% hemoglobin F[2]. This individual was considered to have sickle cell thalassemia. His child was found to have 24% F hemoglobin,

the remainder A and no apparent hematological abnormality. They regarded the latter individual as a case of thalassemia minor of "a non-microcythaemic condition with thalassemia-like features"[5].

In a survey of 2000 Negroes in the Baltimore area, Bradley and Conley found 2 individuals with elevations of F hemoglobin. On extending their study, the same workers found 5 families in which certain members demonstrated elevation of fetal hemoglobin without any apparent hematological abnormality. Fetal hemoglobin levels in their patients ranged from 18 to 33% with a mean of 26%[1].

Herman and Conley have traced the persistence of fetal hemoglobin through 3 generations of a Negro family[3]. There were no clinical or other hematological abnormalities present in these individuals. Fetal hemoglobin levels varied between 24 and 28%. Three members of the family had inherited the gene for hemoglobin S in addition to that resulting in persistence of fetal hemoglobin. These persons appeared to be well and had none of the manifestations of sickle cell anemia. Nevertheless their erythrocytes contained predominantly S hemoglobin and hemoglobin A could not be detected in their red cell hemolysates. These authors attributed the benign nature of this disorder to the high concentration of F hemoglobin in the red cells and the resultant resistance to sickling.

The relationship, if any, to the persistence of fetal hemoglobin and thalassemia is uncertain. If the reported cases represent a variant of thalassemia, the hemoglobin F may be an expression of hemoglobin A suppression by the thalassemia gene. An alternate explanation would be the genetic inheritance of an F gene controlling fetal hemoglobin formation (Went and MacIver[7]).

Summary. During a routine survey an apparently healthy adult was found with an unexplainable 20% content of fetal hemoglobin.

Study of this individual's family reveals 2 of 4 adult siblings with the same finding. This supports the concept that fetal hemoglobin may persist into adult life as a genetic entity without associated hematologic abnormality.

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SUMMARIO IN INTERLINGUA

Persistentia Hereditari de Hemoglobina Fetal

In le curso de un investigation routinari, un apparentemente normal adulto esseva trovate qui habeva un contento inexplicabile de 20% de hemoglobina fetal.

Le studio del familia del subjecto resultava in le mesme constatation in 2 de 4 adulte fraternos de ille. Isto supporta le conception que hemoglobina fetal pote persister usque a etates adulte como un entitate genetic que non es associate con ulle anormalitate hematologic.

TREATMENT OF POLYCYTHEMIA VERA WITH MYLERAN*

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In the lack of causal treatment of polycythemia vera (PCV), the aim of present therapy is to keep the panhemocytosis, particularly the erythremia and thrombocytosis, under control. This can be achieved by suppressing the marrow activity by means of irradiation or myelotoxic agents or, in case of the red cells, by removing the cells from the blood by phlebotomy or hemolysis. In this way the frequency of the most common complications of PCV, thrombosis and hemorrhage, can be reduced (Lawrence[4], Wasserman[7]) whereas there is no evidence that the terminal myelofibrotic or leukemic event which occurs in a substantial number of cases can be avoided by present methods of treatment. Perhaps acute leukemia occurs even more frequently in patients treated with internal irradiation. It remains to be decided, however, whether this is not a manifestation of the increased longevity of patients who have been protected against premature death from thrombosis or hemorrhage (Dameshek and Gunz[2], Lawrence[4], Wasserman[7]).

P_{32} treatment has been used with great success in controlling PCV but nevertheless it has disadvantages. Its use requires special authorization and the usual safeguards involved in every administration of isotopes, and due to its short half life of about 2 weeks it is generally uneconomical to keep in stock. In addition, one is rather frequently encountered with patients previously treated with P_{32} or phlebotomies, or both, in whom the hematocrit is normal but where pronounced thrombocytosis is present. In this situation one is reluctant to administer more P_{32} although it is desirable to reduce the platelet count. The present report deals with treatment of PCV with Myleran and particularly with the effect of this drug on the platelet count.

Methods and Materials. Microhematocrits were done in duplicate. Leukocytes were counted electronically†, and platelets were enumerated according to the method of Brecher and Cronkite[1].

Twelve patients with polycythemia vera were treated. Their age and sex, the duration of the disease, and previous treatment are summarized in Table 1.

Results. Twelve patients with PCV were treated intermittently with Myleran; one patient had 3 courses, 3 had 2 courses, and 8 had one course each. The total dose of Myleran, the duration of treatment, and the hematocrit, leukocyte and platelet count immediately before and after Myleran therapy are tabulated in Table 2. The average total

*Research supported by the U.S. Atomic Energy Commission.
†Coulter Counter, Coulter Electronics, 5227 North Kenmore, Chicago 40, Illinois.

TABLE 1.—TWELVE CASES OF POLYCYTHEMIA VERA: DURATION OF DISEASE AND TREATMENT PRIOR TO FIRST TREATMENT WITH MYLERAN

Patient No.	*Age*	*Sex*	*Color*	*Duration of Disease* (years)*	*Previous Treatment*	
					Phlebotomies	*P_{32} (mC)*
1	48	M	N	8	16	19.25
2	70	F	W	7	35	32.41
3	77	F	W	6	17+	12.28
4	41	M	W	6	17	19.71
5	55	M	W	4	42	yes
6	66	F	W	3	2+	3.3
7	60	M	W	3	8	5.4
8	68	M	W	3	6+	8.91
9	60	M	W	3	29	0
10	72	F	W	2½	9	4.28
11	73	M	W	1½	14	0
12	53	F	W	0	3	0

*From diagnosis to start of Myleran treatment.

TABLE 2.—EFFECT OF MYLERAN ON LEUKOCYTE COUNT, VENOUS HEMATOCRIT AND PLATELET COUNT IN POLYCYTHEMIA VERA.

Patient No.	*On Start of Myleran*			*On Discontinuation of Myleran*			*Duration of Myleran Treatment (Weeks)*	*Total Dose of Myleran (mg.)*
	WBC ($x10^3$)	*Hct.*	*Plat. ($x10^3$)*	*WBC ($x10^3$)*	*Hct.*	*Plat. ($x10^3$)*		
1. (I)	15.8	46.0	707	8.4	42.6	352	5	152
(II)	12.2	52.0	542	6.7	49.0	300	4	168
2. (I)	10.2	44.0	907	5.3	41.0	337	4	140
(II)	8.5	47.0	547	5.9	47.5	360	4	84
(III)	6.7	41.0	522	5.0	43.0	272	3	56
3.	9.9	48.8	742	6.9	47.0	285	5	144
4.	11.2	51.0	580	5.4	48.0	230	5	222
5. (I)	14.7	(53.0)†	700	11.1	(46.5)†	437	12	244
(II)	12.4	(49.5)*	505	7.1	(49.5)*	250	7	182
6.	8.3	(52.5)*	435	3.9	(46.0)*	262	5	224
7.	10.1	41.9	695	7.7	39.6	470	3½	78
8. (I)	12.3	51.2	855	7.8	49.0	330	6	134
(II)	10.0	48.2	415	7.5	50.8	275	4	112
9.	29.6	47.0	870	12.6	46.8	260	10½	376
10.	36.7	47.1	702	21.0	48.1	432	3	80
11.	18.7	62.5	405	10.4	60.5	230	4	162
12.	8.7	47.0	600	6.4	47.0	267	5	196
Mean	13.9	48.2	631	8.2	47.1	315	5.3	162
Range	6.7–36.7	41.0–62.5	405–907	3.9–21.0	39.6–60.5	230–470	3–12	56–376

*1 phlebotomy during Myleran treatment.
†2 phlebotomies during Myleran treatment.
Patients who were phlebotimized during Myleran treatment were excluded from calculation of the mean hematocrit.

dose given during one course was 162 mg. (56 to 376 mg.) and the average duration of treatment was 5.3 (3 to 12) weeks. The platelet count was the main criterion for instituting and discontinuing treatment. In all cases a significant reduction of the platelet count was achieved; concomitantly the total leukocyte count decreased almost to the same degree. In contrast the hematocrit remained essentially unchanged. Bone marrow suppression greater than intended did not occur. Three months after discontinuation of treatment the average leukocyte count had risen slightly whereas the average platelet count still remained at the level reached right after treatment was stopped (Table 3). Only one patient (No. 8) had a definite rise in platelet count during the first 3 months after therapy.

Three patients needed a repeat course of Myleran 4 to 6½ months after the first course and one patient received 3 courses of Myleran 4 months apart. Again significant decreases in platelet and leukocyte counts were observed; the dose response to Myleran appeared to be identical to that of the first course of therapy. Figure 1 shows the effect of treatment in one of these patients.

The present hematological status of the patients is shown in Table 3. It will be seen that an acceptable status exists up to 11 months after Myleran was stopped although it should be noted that phlebotomies have been done as needed to control the hematocrit. One patient (No. 2) died during the study. After radical mastectomy for cancer, a skin graft was done to cover a large

TABLE 3.—FOLLOW-UP OF 12 PATIENTS WITH POLYCYTHEMIA VERA, TREATED WITH MYLERAN.

	Blood Values 3 months after Discontinuation of Myleran							*Status*		
Patient No.	*WBC* ($x10^3$)	*Het.*	*Plat.* ($x10^3$)	*Phlebotomies First 3 Mos. after Myleran*	*Myleran Resumed After (Months)*	*Time Since Last Myleran (Months)*	*Phlebotomies Since Last Myleran*	*WBC* ($x10^3$)	*Het.*	*Plat.* ($x10^3$)
1. (I)	11.1	47.5	345	0	6½	–	1	–	–	–
(II)	–	–	–	0	–	½	0	5.1	47.5	187
2. (I)	8.1	43.2	285	0	4	–	0	–	–	–
(II)	5.9	47.5	342	0	4	–	0	–	–	–
(III)	–	–	–	–	–	Died	0	–	–	–
3.	7.3	44.6	257	0	–	3	0	7.3	44.6	257
4.	7.3	47.7	340	0	–	7	0	6.5	45.5	242
5. (I)	12.0	(53)	397	2	4	–	0	–	–	–
(II)	11.6	(49.5)	275	2	–	3½	3	10.2	46.5	355
6.	5.5	49.0	260	0	–	6	1	4.2	49.5	307
7.	8.9	40.0	420	0	–	11	0	9.1	40.0	472
8. (I)	8.8	52.0	487	0	6	–	2	–	–	–
(II)	8.9	49.0	447	0	–	4	0	8.1	50	377
9.	13.3	(46.2)	272	1	–	8½	4	16.0	45.8	420
10.	–	–	–	–	–	1½	0	18.8	53	312
11.	11.8	(60.2)	172	1	–	11	7	13.2	48.5	240
12.	6.2	42.5	190	0	–	6½	0	7.2	43.0	192
Mean	9.1	–	321	–	–	–	–	–	–	–
Range	5.5–13.3	–	172–487	–	–	–	–	–	–	–

*The hematocrits of patients who had phlebotomies within 3 months after discontinuation of Myleran are given in parentheses.

wound defect. During this time the platelet count rose but since the hematocrit was not elevated it was decided to postpone Myleran in order not to interfere with the "take" of the graft. Later the patient received her third course of Myleran which brought the platelet count down to normal levels. Three weeks after Myleran had been has had to give up work during the observation period.

Discussion. Among previously treated patients with PCV it is not uncommon to see patients with a substantially increased platelet count but a hematocrit within normal limits. In such cases attempts to eliminate the thrombocytosis with P_{32} may result in an unneces-

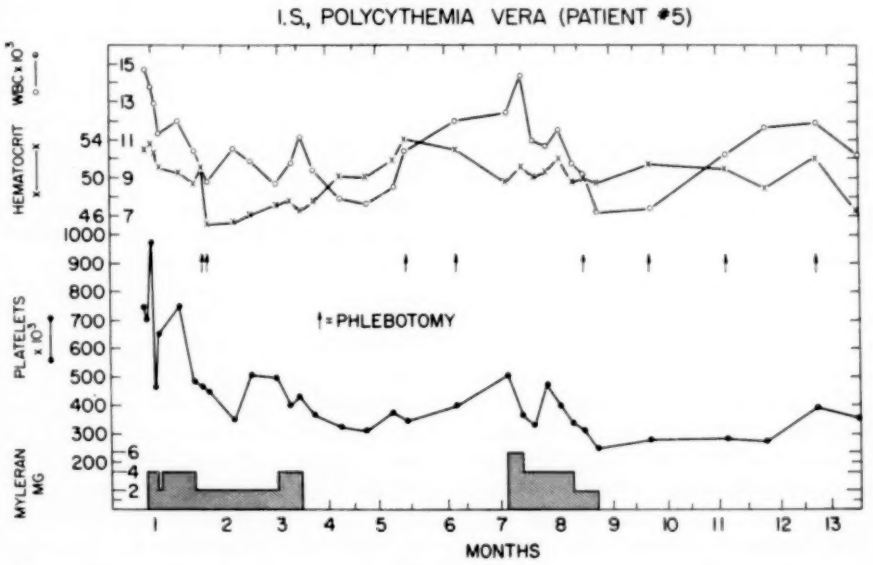

Fig. 1.—Effect of Myleran treatment on blood counts in patient with polycythemia vera (patient No. 5).

discontinued and while the platelets and hematocrit were normal, the patient died from massive pulmonary embolism. This was the only thrombotic complication in this series after initiation of Myleran therapy. Some of the patients had had thromboses before being referred to us, apparently due to inadequate treatment.

One patient (No. 5) who, prior to Myleran treatment, was unable to work because of repeated splenic infarcts and insomnia due to severe paresthesias has returned to work on disappearance of these symptoms. None of the patients

sary and undesirable depression of erythropoiesis. From the present data, Myleran appears to be very helpful in this situation. At the beginning of Myleran treatment, only one patient (No. 11) had a definitely increased hematocrit whereas all of the patients had thrombocytosis, most of them in excess of 500,000 platelets per c.mm. With no exception a significant reduction in platelet count was achieved whereas the hematocrit showed little or no change. In all but one patient (No. 8), the platelets remained at the immediate post treatment level 3

months after Myleran had been discontinued. The platelet count remained in the "safe" range, which arbitrarily has been defined as less than 500,000 platelets per c.mm. provided that the hematocrit is within normal limits, for up to 11 months after treatment.

Generally, although not consistently Myleran therapy has been started when the platelet count exceeded 500,000 per c.mm. Usually the initial daily dosage has been 4 to 6 mg.; the highest daily dose given was 8 mg. The patients were then seen weekly, and when the platelets started to decline the dose was tapered off to 4 or 2 mg. per day. In this connection more emphasis was laid on the slope of the decrease in platelet count than on the absolute count. Used in this way, Myleran had only a slight or no delayed effect. In one patient (No. 6) the leukocyte count was slightly subnormal (3900 per c.mm.) when the desired platelet reduction had been reached and in another patient (No. 7) treatment was stopped when the hematocrit decreased from 41.9 to 39.6 although the platelet count of 470,000 at this time would have motivated slightly longer treatment. Thus no serious bone marrow toxicity occurred in this series. No attempts were made to push Myleran to beginning toxicity although somewhat longer lasting results could probably have been achieved in this way, as pointed out by Wald, Hoshino and Sears[6]. Attempts to slightly overtreat with Myleran might jeopardize one of the advantages of this drug over P_{32}, which is that when Myleran is used cautiously it is possible to "titrate" the effect very closely because further bone marrow suppression does not occur when the drug has been discontinued.

In contrast to the present series, Wald, Hoshino and Sears[6] with Myleran obtained considerable reductions not only of the leukocyte and the platelet counts but also of the hematocrit. Two explanations are at hand: the total doses given by them were generally higher than in this series, and the hematocrit before treatment was also higher than typical of this series. Perhaps the sensitivity to Myleran increases with the proliferative activity of a cell series.

Louis[5] has reported on Myleran treatment of 18 polycythemic patients; at the onset of therapy the hematocrits ranged from 47 to 70% whereas after treatment the hematocrit was in the normal range in all patients. It does not appear from the report to what extent phlebotomies, which were performed during Myleran therapy, contributed to this result. The leukocyte count was lowered in each instance; data concerning platelets were not given. The average total dose during initial treatment appears to be considerably higher than in the present series, and in addition all but 2 of the patients received maintenance therapy (2 to 18 mg. per week) after remission had been obtained. Two of the patients developed severe pancytopenia. In both instances this resulted from attempts to keep the hematocrit in check with Myleran which for this reason was given over a prolonged period of time or in large doses. It is noteworthy that the pancytopenia progressed for 5 to 13 weeks after therapy had been discontinued in both cases. This indicates that the hematocrit cannot always safely be controlled with Myleran alone. In our experience the rapidity with which the platelet and leukocyte counts fall is the safest guide for Myleran dosage and duration of treatment. A rapid decline in hematocrit with a less pronounced fall in platelets and leukocytes would of course also indicate caution or complete cessation of treatment but from the present data this latter sequence of events appears to be uncommon. In our opinion Myleran should not be pushed to toxicity

in order to control the hematocrit. This can easily be achieved by supplementing Myleran with phlebotomies, as done in this series. Naturally, if phlebotomies must be performed very frequently, treatment with P_{32} will be preferable.

It remains to be decided whether Myleran can or should replace P_{32} as the therapeutic method of choice in PCV. It will probably be possible to control most cases of polycythemia vera with Myleran combined with phlebotomies. The need of phlebotomies subtracts from the merits of Myleran treatment but it must be borne in mind also that P_{32} treatment is often supplemented with phlebotomies, even by outspoken protagonists of P_{32} (Lawrence[4]). It may be a disadvantage of Myleran that during a course of treatment the patients must be controlled weekly, although with some experience bi-weekly blood studies would appear adequate, but again this does not differ too much from the need of control with cautious P_{32} therapy (Lawrence[4]). If P_{32} induced remissions tend to last longer than Myleran induced remission, however, the patients in the long run of course will have to be seen more often than with P_{32}. It is also conceivable that resistance to Myleran may develop after repeated courses of treatment although so far there has been no evidence pointing in this direction. The well established leukemogenic effect of radiation would appear to be in favor of Myleran treatment. It must be remembered, however, that Myleran may also be carcinogenic (Koller[3]).

The advantages of Myleran are that it is inexpensive, that it can be kept in stock for use at any time, that its effect can be accurately "titrated," and that it can be administered by any interested physician with access to reliable blood counts. The latter point may be regarded a disadvantage by some in the sense that treatment of PCV may become too decentralized. Finally, it is a major advantage of Myleran that it can safely be given in the presence of a normal hematocrit in order to bring an existing thrombocytosis under control; in this respect Myleran represents a valuable expansion of the therapeutic possibilities in PCV.

Summary. Twelve patients with polycythemia vera received a total of 17 courses of Myleran treatment. The average total dose was 162 (56 to 376) mg. and the average duration of a course of treatment was 5.3 (3 to 12) weeks. Significant reductions in platelet counts resulted in all patients, with a decrease in the mean platelet count from 631,000 to 315,000 per c.mm. The leukocyte count showed a similar decline in all patients. No, or only small, changes occurred in the hematocrit values; it may be pertinent in this respect that only one of the patients had a definitely elevated hematocrit before treatment. The platelets remained at the immediate post-treatment level 3 months after cessation of therapy in all patients but one. The platelet count has stayed below 500,000 per c.mm. for up to 11 months after treatment. No undesired bone marrow suppression was observed in this series.

The final role of Myleran in the treatment of PCV remains to be determined. At the present time Myleran appears to be the treatment of choice to control thrombocytosis in the presence of a normal or near normal hematocrit.

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SUMMARIO IN INTERLINGUA

Tractamento de Polycythemia Ver con Myleran

Dece-duo patientes con polycythemia ver recipeva un total de 17 cursos de therapia a Myleran. Le dose total medie esseva 162 mg (56 a 376), e le duration medie del cursos de therapia esseva 5,3 septimanas (3 a 12). Reductiones significative del numeration de plachettas resultava in omne le patientes, resultante in un reduction del numeration medie de plachettas ab 631.000 a 315.000 per mm^3. Le numeration del leucocytos monstrava un simile declino in omne le patientes. Nulle (o solmente micre) alterationes occurreva in le valores del hematocrite. Il es possibilemente de interesse in iste connexion que solmente un del patientes habeva un definitemente elevate hematocrite ante le tractamento. Le plachettas manteneva le nivello immediatemente post-tractamental durante tres menses post le cessation del therapia in omne le patientes excepte un. Le numeration del plachettas remaneva infra 500.000 per mm^3 durante periodos de usque a 11 menses post le tractamento. Nulle non-desirate suppression de medulla ossee esseva observate in iste serie.

Le rolo definitive de Myleran in le tractamento de polycythemia ver remane a determinar. Al tempore presente, Myleran pare esser le tractamento de election pro subjugar thrombocytosis in le presentia de hematocrite normal o quasi normal.

COMPARISON OF THE VALUE OF SEVERAL SEROLOGICAL TESTS IN RHEUMATOID DISEASE

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AND

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Over the past 20 years a large and increasing number of agglutination techniques have been applied to the sera of patients with rheumatoid disease. The capacity of these sera to agglutinate sensitized particulate bodies has been demonstrated with bacteria, erythrocytes, collodion particles, latex particles and colloidal clay. The property of these sensitized particles to agglutinate is probably dependent in every instance on the presence in the serum of an identical factor, which is, with a few exceptions, limited to the serum of patients with rheumatoid disease. While the sensitivity of the various tests has become reasonably uniform, laborious and complicated techniques have limited the applicability of the procedure. With the recent introduction of a simple, rapid method (RA test) which could be used in the average laboratory, we felt that substantiation of reliability of the test was necessary prior to acceptance. The latex-fixation, the bentonite flocculation and the latex-globulin modification (RA test) tests were performed on 182 patients, 57 of whom had rheumatoid disease, 99 had a variety of rheumatic disorders and 26 were controls without any form of rheumatic disease.

The rheumatoid factor responsible for the agglutination phenomenon has been extensively and intensively sought not only as a diagnostic advantage but also as the possible key to the elucidation of the pathogenesis of the disease. It is believed to be contained in fraction III of serum and is largely beta globulin but has small amounts of alpha and gamma globulin and a trace of albumin (Heller *et al.*[6]). Electrophoretically (Lamont-Havers[9]), both by paper and convection, the factor is in or near the gamma globulin. This has caused some investigators (Miller, Lynch and Lansbury[10], Wallis[16]) to regard the rheumatoid agglutinating activity as completely nonspecific in the immunological sense, but rather some undefined instability of specific serum proteins. Others (Kunkel, Franklin and Muller-Eberhard[8]) have presented preliminary evidence which suggests that rheumatoid factor may be an auto-antibody against modified gamma globulin.

In 1940, a report by Waaler[15] first drew attention to the ability of rheuma-

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toid sera to agglutinate sensitized red cells, but the application of this phenomenon as a diagnostic test was not considered feasible until publication of the work of Rose and co-workers in 1948[13]. In 1949 and 1952, Heller and associates[3,5] modified the test of absorbing the heterophil antibody by absorption of sera with packed sheep red cells, thereby eliminating the necessity for measurement of differential agglutination, the titer being read directly against sensitized cells. Later they (Jacobson *et al.*[7]) proposed that the inhibition of sensitized cell agglutination by normal human gamma globulin and the agglutination, by rheumatoid serum, of tannic acid-treated sheep cells to which gamma globulin had been absorbed indicated an antigen-antibody-like reaction in which there was the likely presence of a heterogenetic antibody.

Following the demonstration by Waaler and Rose that the agglutinating activity of rheumatoid serum was concentrated in the globulin fraction, Winblad[17] reported the presence of an inhibitory substance peculiar to the reaction and Heller and co-workers[4] felt that the substance was present entirely in fraction II or gamma globulin. It was postulated that the gamma globulin inhibited agglutination by competing with the sensitized sheep cell for the rheumatoid factor (Jacobson *et al.*[7]).

Singer and Plotz[14], observing that tannic acid treated red cells could be sensitized by human gamma globulin, deduced that an essential feature of the agglutination phenomenon was a reaction between a constituent of the gamma globulin on the cell surface and the rheumatoid factor. As a result, they investigated the agglutination of polystyrene latex particles coated with gamma globulin. This procedure eliminated the difficult and time-consuming process of absorption and inactivation of test sera and offered a relatively simple procedure that could be adapted to clinical screening.

In 1957 at the Ninth International Congress on Rheumatic Diseases, Bunim *et al.*[1,2] introduced a method employing bentonite (colloidal clay) as the absorptive particulate material which was sensitized by human gamma globulin (Fraction II) and then mixed with patients' serum.

In 1958 a simple, rapid slide test*, a modification of the latex fixation method, utilizing an indicator already coated with reactant (latex-globulin reagent) became available. The technique for this test is simple and can be performed in less than 5 minutes.

Methods and Materials. The original procedures used and recommended by the authors were employed without alteration. Clinical material consisted of 182 patients; 57 patients had rheumatoid disease, 4 in Stage I (ARA classification), 14 in Stage II, 7 in Stage III and 2 in Stage IV; 99 patients exhibited some form of rheumatic disorder other than rheumatoid disease; and 26 patients, with no rheumatic disease, served as controls.

LATEX-GLOBULIN MODIFICATION TEST (RA TEST, HYLAND LABORATORIES). Materials for this test are commercially available as a kit which contains: a latex-globulin reagent prepared from polystyrene latex and human gamma globulin; positive control serum (rheumatoid serum in a dilution of 1:20); negative control serum (normal human serum); glycine-saline buffer diluent (a sterile solution of glycine and sodium chloride at pH 8.2); and a slide divided in 6 equal squares allowing the performance of 6 tests at any one time.

A 1:20 dilution of the serum to be tested was prepared by adding one drop of the serum to 1 ml. of glycine-saline buffer diluent. One drop of diluted serum specimen is placed on the divided slide, to this one drop of latex-globulin reagent was added and mixing was accomplished with an applicator. Positive and negative controls were

*RA test (Hyland Laboratories, 4501 Colorado Boulevard, Los Angeles 39, California).

prepared, each with one drop of appropriate control serum mixed with one drop of latex-globulin reagent. The slide was tilted from side to side for one minute and then observed for macroscopic clumping. In positive tests, visible flocculation usually occurred in a few seconds.

BENTONITE FLOCCULATION TEST. Ten milliliters of bentonite* suspension was centrifuged and the sediment resuspended in 1 ml. distilled water. To this suspension 2 ml. of veronal buffered Fraction II† solution was added and the two components gently mixed by tilting and rotating. The suspension was then allowed to stand for 15 to 30 minutes at room temperature; then 15 ml. of distilled water were added, the suspension was gently mixed again, then centrifuged for 5 minutes at 3,000 r.p.m. and the sediment resuspended in 15 ml. of water and vigorously shaken for 30 seconds. This suspension was centrifuged again, and the sediment resuspended in 5 ml. of water. One milliliter of 0.1% methylene blue solution was added and again vigorously shaken. After 5 minutes, 10 ml. of water were added, the suspension centrifuged, and the sediment resuspended in 10 ml. of distilled water and centrifuged. Washing was repeated once more and the sediment diluted in 4 ml. of 0.05 molar phosphate buffer at pH 7.3. To this sensitized bentonite suspension 0.1 ml. of 1% Tween 80‡ was added. The serum to be tested was inactivated for 30 minutes at 56° C. Microscopic slides (3″ × 2″) with 12 rings were used to perform the tests. Into each ring on the slide 0.1 ml. of serial twofold dilutions of serum in saline and one drop of sensitized bentonite suspension were placed. The slide was then rotated on a Boerner-type rotating machine, 100 to 120 times per minute for 20 minutes, and read microscopically immediately at low-power magnification. The bentonite flocculation test was considered positive when two plus or stronger clumping occurred in a serum dilution of 1:32 or higher.

LATEX FIXATION TEST. A suspension of Polystyrene latex 0.81 micron in diameter§, boric acid-sodium hydroxide in saline buffer at pH 8.2 and a 1% solution of lyophylized Fraction II gamma globulin are required. To 0.5 gm. of lyophylized Fraction II, borate in saline buffer in 5 to 10 ml. increments was added mixing well each time and saving the supernatant until a total of 100 ml. had been added and the powder completely dissolved. Antigen consisted of 0.1 ml. of latex stock solution, 9.4 ml. of borate buffer and 0.5 ml. of the 0.5% human gamma globulin stock solution.

The serum to be tested was diluted in this borate saline buffer with dilutions ranging from 1:20 to 1:5120. A control tube containing 1 ml. of borate saline buffer without added serum was included in each test. To each serum dilution tube and to the control, 1 ml. of the borate saline-latex-gamma globulin antigen was added; the tubes were then thoroughly shaken and incubated in a water bath at 56° C. for 2 hours. The tubes were then centrifuged at 2300 r.p.m. for 3 minutes and the resultant visible agglutination ranging from negative to 4 plus was read with the naked eye. Agglutination in a dilution greater than 1:20 was considered positive.

Results. In Table 1, the latex-globulin (RA) modification test, the latex-fixation test and the bentonite flocculation test were performed on the sera of 60 consecutive patients. Twenty-two patients with clinically evident rheumatoid disease were tested; the 18 with positive tests were in Stages II, III and IV, the 4 with negative tests were

TABLE 1.—RA (LATEX-GLOBULIN TEST IN 60 CONSECUTIVE CASES

Group of Cases	*Positive Test*	*Negative Test*
Rheumatoid disease	18+	4*
Nonrheumatoid rheumatic	1	31
Nonrheumatic control	0	6
TOTALS	19	41

+All cases were positive with the Latex Fixation and Bentonite Flocculation Tests.

*'RA'—negative tests on 4 patients with rheumatoid disease had negative tests with the Latex Fixation and Bentonite Flocculation Tests on different occasions.

*Volclay (Wyoming bentonite) No. 200 standard. Available from American Colloid Company, Merchandise Mart Plaza, Chicago 54, Ill.

†American Red Cross, Washington, D.C.

‡Atlas Powder Company, Wilmington, Delaware.

§Dow Chemical Company, Midland, Michigan.

in Stage I. Of the 32 patients with a rheumatic disorder other than rheumatoid disease, 31 were negative and one positive by all methods; the single positive was on the serum of a patient with rheumatic fever. Six patients without any form of rheumatic disease had negative tests.

Table 2 shows the results of the latex-fixation and the bentonite tests on the sera of 35 patients with rheumatoid disease. Twenty-seven (75%) showed positive agglutination, while 9 (25%) were negative. Positivity appears to be most likely in Stages II and III (ARA classification) while the tests seem less sensitive in Stages I and IV and in the atypical variants of the disease.

TABLE 2.—LATEX FIXATION AND BENTONITE FLOCCULATION TESTS IN 35 CASES OF RHEUMATOID DISEASE

Stage of Disease (ARA classification)	*Positive test (both methods)*	*Negative test (both methods)*
I*	4	5
II	14	0
III	7	2
IV	2	2
TOTALS	27 (75%)	9 (25%)

*One case gave negative result on one occasion and positive result when repeated two months later.

Table 3 demonstrates the relative infrequency of false positive reactions noted among 67 patients with a variety of rheumatic diseases exclusive of rheumatoid disease. Two patients with the clinical diagnosis of rheumatic fever and 2 with palindromic rheumatism gave positive tests; the remaining 63 were negative.

Table 4 illustrates the almost complete negativity of the sera of 20 nonrheumatic controls.

TABLE 3.—LATEX FIXATION AND BENTONITE FLOCCULATION TESTS IN 67 CASES OF NONRHEUMATOID RHEUMATIC DISEASES

Diagnosis	*Positive test (both methods)*	*Negative test (both methods)*
Gout	0	5
Rheumatic fever	2	5
Postural arthropathy	0	1
Ankylosing spondylitis	0	13
Degenerative joint disease	0	15
Reiter's disease	0	5
Periarteritis nodosa	0	1
Systemic lupus erythematosus	0	6
Fibromyalgia	0	1
Diffuse scleroderma	0	1
Psychogenic rheumatism	0	4
Palindromic rheumatism	2	0
Post-rubella arthritis	0	1
Trichinosis	0	1
Tenosynovitis	0	2
Infectious arthritis	0	1
Traumatic arthritis	0	1
	4	63

TABLE 4.—LATEX FIXATION AND BENTONITE FLOCCULATION TESTS IN 20 NONRHEUMATIC CONTROLS

Diagnosis	*Positive test (both methods)*	*Negative test (both methods)*
Tuberculosis	0	1
Arteriosclerotic heart disease	0	2
Nephrosis	0	1
Hypertensive cardiovascular disease	0	2
Bronchogenic carcinoma	0	1
Hodgkin's disease	0	1
Ulcerative colitis	0	2
Peptic ulcer	0	2
Gastrointestinal disturbance	0	1
Diabetes mellitus	0	3
Myocarditis, nonrheumatic	0	1
Acute cholecystitis	0	1
Neurasthenia	1	0
Acute glomerulonephritis	0	1
	1	19

Discussion. From the data presented in the foregoing tables it appears that the latex fixation, the latex-globulin modification (RA test) and the ben-

tonite flocculation tests which we employed show a fairly high degree of specificity for rheumatoid disease in Stages II and III, but offer limited corroborative assistance in the diagnosis of Stage I and variants of rheumatoid disease.

Unfortunately, patients with early or atypical variants of rheumatoid disease present the most puzzling diagnostic problems. Here is the area in which the greatest possible contribution to accurate identification of the illness could be rendered by reliable laboratory test. Ragan[11] has stated, "the specificity of the agglutination reactions is dependent primarily upon clinical judgment. The diagnosis of rheumatoid disease in its early stages or in atypical disease is difficult, varies from institution to institution and in many instances depends upon the personal whim of the examiner."

When the patient with rheumatoid disease has progressed to the point where the historical and physical findings conform to the *definite* type of the American Rheumatism Association[12] the diagnosis is usually quite clear-cut without reference to predictable alterations in serology and laboratory confirmation becomes meaningless.

The cause or causes of this disorder are unknown and there is no specific pathological abnormality which reveals the presence of the disease. In fact it is only in recent years that the systemic nature of this disorder has been acknowledged and pathogenetic concepts have ranged from reaction to stress to response to auto-immune mechanisms. Some experienced workers in the field of rheumatic diseases express doubt about the homogeneity of the disease which is presently clinically diagnosed as rheumatoid arthritis.

Summary and Conclusions. A total of 302 latex and bentonite tests have been performed on the sera of 122 patients. The sera of 32 individuals were positive with both tests, 90 were negative and one patient was positive initially, but followup tests were negative. The latex globulin (RA) test, performed on 60 consecutive cases, correlated well with the latex fixation and bentonite flocculation tests done on the sera of the same patients at the same time.

The mechanisms of these serological reactions are not well understood. Present concepts suggest that the various particles employed act as inert carriers for a component of gamma globulin with which the rheumatoid factor reacts and that there is an inhibitor of this reaction present in all normal human sera. Continuing development and refinement of procedures will undoubtedly provide a practical laboratory method in the near future and will contribute materially to our understanding of the pathogenesis of rheumatoid disease.

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SUMMARIO IN INTERLINGUA

Comparation del Valor de Plure Tests Serologic in le Studio de Morbo Rheumatoide

Un total de 302 tests a latex e a bentonite esseva effectuate con le seros de 122 patientes. Le seros de 32 individuos esseva positive in ambe tests; 90 esseva negative; e 1 esseva positive al initio, sed tests de repetita in iste caso esseva negative. Le test de globulina a latex esseva effectuate in 60 casos consecutive e se monstrava in bon correlation con le test de fixation a latex e le test de flocculation a bentonite le quales esseva effectuate in le seros del mesme patientes al mesme tempore.

Le mechanismos de iste reactiones serologic non es ben comprendite. Currentemente nostre conception es que le varie particulas empleate age como vectores inerte de un componente de globulina gamma con le qual le factor rheumatoide entra in reaction e que il existe un inhibitor de iste reaction in omne normal seros human. Le continue disveloppamento e raffinamento del methodologia technic va sin dubita resultar proximemente in un practic routine de laboratorio e contribuer substantialmente al avantiamento de nostre comprension del pathogenese de morbo rheumatoide.

SUMMARIO IN INTERLINGUA

(See page 235 for original article)

Difficultates Diagnostic in Hyperthyroidismo

Hyperthyroidismo es non semper facile a recognoscer. Isto vale specialmente pro subjectos de etates plus avantiate. Le typic symptomas de hypermetabolismo e struma pote esser mascate in parte per le exaggeration de gravamines que ha lor base in un systema organic. In casos sporadic il occurre que nulle del symptomas classic es evidente, e le diagnose depende alora del saper que le morbo pote manifestar se sub varie formas inusual. Es presentate tres casos que sublinea iste difficultates.

THE RELATIONSHIP OF BRUCELLA INFECTION TO BIOLOGIC FALSE POSITIVE TESTS FOR SYPHILIS

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Subsequent to the discovery of a serologic test for syphilis by Wassermann, Neisser, and Bruck in 1906[10], it was recognized that the serum from patients with diseases or conditions other than syphilis might show a biologic false positive (BFP) test (Rein and Elsberg[6]). Such reactions are immunologically nonspecific, inasmuch as the serologic tests for syphilis (STS) utilize either extracts of normal mammalian tissue or cardiolipin as antigens rather than *Treponema pallidum* or its chemical fractions.

Prior to 1949, specific tests for the diagnosis of syphilis were not available to exclude BFP reactions and for their accurate differentiation from latent syphilis in patients with no history or clinical manifestations of the disease. Thus, presumptive evidence only indicated that malaria, leprosy, infectious mononucleosis, and infrequently, certain other diseases might be responsible for BFP reactions.

In 1949, Nelson and Mayer described the *Treponema pallidum* immobilization (TPI) test, a specific technique utilizing *T. pallidum* as the antigen[4]. With this procedure, conclusive evidence was established that diseases and conditions other than syphilis could elicit a reactive STS (Nelson *et al.*[5]). In addition, some individuals with no clinical disease were discovered to be BFP reactors. It is now known that such reactivity precedes the onset of chronic illness in certain patients (Moore and Mohr[3]).

Although *Brucella* infection was considered to be responsible for some BFP reactions (Scott *et al.*[7]), data have not been available to confirm the validity of the concept. This report presents the prevalence of *Brucella* infection among BFP reactors as determined by the agglutination and intradermal tests.

Methods and Materials. Agglutination tests for Brucella infection were carried out according to the technique recommended by the Committee on Brucellosis of the National Research Council employing the *Brucella abortus* antigen prepared by the Bureau of Animal Industry of the U.S. Department of Agriculture, Beltsville, Maryland. Intradermal tests with 0.1 ml. of Brucellergen (Rein and

Elsberg[6]) were performed after blood had been obtained for the serologic tests. The TPI test was carried out according to the method of Nelson and Mayer[4] with the modifications of Magnuson and Thompson[2], Thompson and Magnuson[8], and Boak and Miller[1]. The VDRL and Cardiolipin Kolmer complement fixation tests STS, were completed at the laboratory of the Los Angeles City Health Department according to the method described in the Manual for Serologic Tests for Syphilis[9].

The agglutination test was carried out on a total of 2034 sera, of which 464 were STS and TPI reactive (Syphilis group), 1126 STS reactive and TPI nonreactive (BFP group), and 444 STS and TPI nonreactive (Normal group). Intradermal tests with Brucellergen were carried out on 278 patients, 33 of whom were classified in the Syphilis group, 45 in the BFP group, and 200 in the Normal group.

Results. Brucella agglutinins, ranging in titer from 1:20 to 1:5120, occurred in 98 or 21.1% of 464 sera from the Syphilis group and in 327 or 29.0% of 1126 sera from the BFP group. Only 46 or 10.4% of 444 sera from the Normal group showed positive agglutination tests (Table 1). The 10.7% higher incidence of agglutinins in the Syphilis group as compared to the Normal group, as well as the 18.6% increased incidence in the BFP group as compared to the Normal group, is significant at the 0.001 level. The data suggest that patients with syphilis and those with BFP reactions have a significantly higher incidence of Brucella agglutinins than does a non-hospital population, that is, the Normal group. They further indicate a possible relationship between Brucella infection, as designated by the agglutination test, and the presence of reagin in the serum of patients with either syphilis or with a BFP reaction. The difference between the incidence of Brucella agglutinins in the Syphilis group (21.1%) and in the BFP group (29.0%) is not significant (Table 1).

TABLE 1.—*BRUCELLA* AGGLUTININS IN SYPHILITIC, BIOLOGIC FALSE POSITIVE, AND NORMAL SERA

			Brucella Agglutinins		
Classification	*STS*	*TPI*	*Total Sera*	*Number Positive*	*% Positive*
Syphilis group	+	+	464	98	21.1
BFP group	+	—	1126	327	29.0
Normal group	—	—	444	46	10.4

An intradermal test with Brucellergen was carried out on patients from each group because of its greater specificity in the detection of past or present Brucella infection than that of the agglutination test. Dermal sensitivity was observed in 12 or 36.4% of 33 patients in the Syphilis group and in 21 or 46.7% of 45 patients in the BFP group. Only 19 or 9.5% of the 200 patients in the Normal group had positive intradermal reactions (Table 2). The significant difference in dermal sensitivity between the Syphilis and Normal groups and between the BFP and Normal groups supports the specificity of the agglutination test, and further suggests a relationship between Brucella infection and the presence of reagin in the serum of patients with and without syphilis. The difference observed between the 36.4% incidence of dermal sensitivity to Brucella in the syphilis

group and the 46.7% incidence in the BFP group likewise was not significant (Table 2). The data confirm the results obtained with the agglutination test on serum from both groups.

Discussion. These data show a significant relationship between evidence of past or present Brucella infection and the presence of reagin in the serum of patients with or without syphilis, based upon serologic and intradermal tests for brucellosis. Of special significance are absorption studies now in progress in order to determine whether a relationship exists between antigens of *Brucella abortus* and antigens of *Treponema pallidum*. Observation on a limited number of human sera from BFP reactors have demonstrated that reagin can be absorbed with *Br. abortus*. The possible stimulation of reagin formation by Brucella as well as by *T. pallidum* suggests the hypothesis that reagin in the serum of patients with syphilis may be formed not only in response to *T. pallidum* but also to Brucella and possibly to other infectious agents. Concurrent Brucella infection may be responsible for the failure of sero-reversal in patients adequately treated for syphilis. Search for other underlying diseases as the cause of continued reagin stimulation should be undertaken.

TABLE 2.—DERMAL SENSITIVITY TO *BRUCELLA* IN SYPHILITIC AND BFP PATIENTS AND IN NORMAL INDIVIDUALS

			Incidence of Intradermal Reactions		
Classification	*STS*	*TPI*	*Total Patients*	*Number Positive*	*% Positive*
Syphilis group	+	+	33	12	36.4
BFP group	+	—	45	21	46.7
Normal group	—	—	200	19	9.4

Summary and Conclusions. 1. Brucella agglutinins, ranging in titer from 1:20 to 1:5120, occurred in 98 or 21.1% of 464 sera from patients with past or present syphilis and in 327 or 29.0% of 1126 sera from biologic false positive reactors. Only 46 or 10.4% of 444 sera from normal individuals showed the presence of Brucella agglutinins.

2. Dermal sensitivity to Brucella occurred in 12 or 36.4% of 33 patients with present or past syphilis and in 21 or 46.7% of 45 patients with BFP reactions. Only 19 or 9.5% of 200 normal individuals exhibited dermal sensitivity to Brucella.

3. The data point toward an antigenic relationship between *Brucella abortus* and *Treponema pallidum*. The observations further suggest that in certain patients reagin formation may be due to infection with Brucella.

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SUMMARIO IN INTERLINGUA

Le Relation Inter Infection per Brucella e False Positivitate in Tests pro Syphilis

1. Agglutininas de Brucella—in titros de inter 1:20 e 1:5120— occurreva in 98 de 464 seros (21,1%) ab patientes con syphilis passate o presente e in 327 de 1126 seros (29,0%) ab falsemente positive reactores biologic. Solmente 46 de 444 seros (10,4%) ab individuos normal monstrava le presentia de agglutininas de Brucella.

2. Sensibilitate dermal pro Brucella occurreva in 12 de 33 patientes (36,4%) con syphilis passate o presente e in 21 de 45 patientes (46,7%) con reactiones biologic falsemente positive. Solmente 19 de 200 normal subjectos (9,5%) exhibiva sensibilitate dermal pro Brucella.

3. Le datos pare signalar un relation antigenic inter *Brucella abortus* e *Treponema pallidum*. Le observationes etiam suggere que in certe patientes le formation de reagina es possibilemente activate per infection brucellic.

DIAGNOSTIC DIFFICULTIES IN HYPERTHYROIDISM

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The classic signs and symptoms of hyperthyroidism are well known, and typical cases offer no problem in diagnosis. Many cases, on the other hand, have been described in which there were atypical or unusual manifestations. While the more typical features were usually apparent following closer examination, diagnosis was often delayed by initial attention to the more apparent complaints (Chapman and Maloof[3]). There is a much smaller group of individuals with hyperthyroidism who present with no evidence of hypermetabolism or enlargement of the thyroid gland. Diagnosis in these cases may be quite difficult unless the physician is constantly cognizant to the possibility of this disease presenting in an unusual form. Inasmuch as hyperthyroidism can be adequately treated with excellent results (Hamwi and Goldberg[5], McCullagh[8]), even keener awareness of this diagnostic possibility is demanded. Such unusual manifestations seem to us to be especially common in older individuals. Several representative cases have been selected for presentation.

Diagnosis in two of the cases was established on the basis of abnormalities in both the protein-bound iodine levels and I_{131} uptake determinations. In the third case, facilities for radioisotope studies were not available and serum for protein-bound iodine was not obtained prior to institution of therapy. However, kinemometric measurement of the free Achilles-tendon reflex as described by Lawson[7] revealed values characteristically seen in hyperthyroidism. This finding, plus the dramatic response to anti-thyroid medication, would seem to justify the diagnosis of hyperthyroidism in this case.

Case Reports. CASE 1. A 63-year-old white woman was admitted to the hospital on 20 March 1957 because of palpitations and a fast pulse. Symptoms had begun abruptly 6 hours previously and were associated with tachypnea and profuse diaphoresis. There had been no previous cardiac symptoms except for occasional tightness in the chest following strenuous exertion. There were no complaints suggestive of hypermetabolism. System review was otherwise not contributory. Past history revealed therapy for carcinoma of the cervix in 1953 and surgical removal of a renal stone in the same year.

Physical examination revealed a well-developed, well-nourished, apprehensive white woman. Apical pulse 180 per minute, blood pressure was 110 systolic, 46 diastolic, weight 122 pounds. The thyroid was not enlarged. The heart appeared slightly enlarged with the point of maximum cardiac impulse 2 cm. outside the midclavicular line in the 5th intercostal space. There was a soft, blowing systolic murmur at the apex. Liver was palpable 2 cm. below the right costal margin and was nontender. Peripheral pulses were normal. Neurological examination was normal.

Laboratory data revealed a normal white blood cell count, hemoglobin 10 gm. per 100 ml., hematocrit 31, normal urinalysis and non-reactive serological test for syphilis. Cardiac fluoroscopy was normal; an electro-

cardiogram showed atrial fibrillation with a rapid ventricular response. A protein-bound iodine was performed; however, the specimen was drawn following an intravenous pyelogram and the reported elevation was interpreted as a factitious one due to the previous iodine administration.

Following admission she was rapidly digitalized and normal rate and rhythm were quickly restored. In the absence of other obvious pathology, she was placed on maintenance digitalis therapy and discharged to outpatient follow-up on 3 April 1957. She developed signs of digitalis toxicity and discontinued the drug completely without returning to the clinic for follow-up. When finally seen on 26 April she complained of recurrent palpitations, 16-pound weight loss, progressive weakness and nervousness. Physical examination at this time revealed an apprehensive, chronically ill woman. Blood pressure 200 systolic, 50 diastolic; apical pulse rate 150 per minute, radial pulse rate 120 per minute. The neck was bulging and the thyroid was markedly enlarged, firm and non-tender. There was a fine tremor of the hands and hyperactive deep tendon reflexes, but no other signs of hyperthyroidism. Laboratory data showed normal white blood cell count, hemoglobin 12.8 gm. per 100 ml., hematocrit 38. Urinalysis showed many white blood cells per high powered field. Serum cholesterol was 250 mg. per 100 ml. Protein-bound iodine was 13.2 μg. per 100 ml. Electrocardiogram again showed atrial fibrillation. Radioactive I_{131} studies showed 49.4% uptake in 2 hours and 80.3% uptake in 24 hours. She was given 6.97 millicuries of I_{131} and 4 days later was placed on propylthiouracil. At the time of discharge, on 25 May 1957, she showed marked improvement with loss of previous symptoms, weight gain of 14 pounds and maintenance of normal cardiac rhythm. Following discharge, she has continued to do well with no recurrence of symptoms.

COMMENT. This case is one of hyperthyroidism which presented as cardiac disease with atrial fibrillation and which responded quickly to digitalization. Initally there was no thyroid enlargement or evidence of hypermetabolism. A recurrence of the cardiac difficulty along with more classical symptoms led to rehospitalization and adequate therapy which has subsequently returned the patient to normal activity. Although there is probably underlying cardiac disease in this case, it seems likely that the overt manifestations were precipitated by increased thyroid hormone activity.

CASE 2. A 65-year-old Malayan male was admitted to the hospital because of anorexia and weight loss. Symptoms had developed one month previously, and he had subsequently experienced orthopnea and paroxysmal nocturnal dyspnea. For the week preceding admission he noted swelling of the ankles and squeezing left precordial pain which was relieved by rest. There were no manifestations of hypermetabolism. System review was otherwise non-revealing. Past history revealed only that he had pneumonia with pleurisy in 1953.

Physical examination revealed a poorly nourished, chronically ill man. Blood pressure 134 systolic, 60 diastolic, pulse rate 98 per minute, weight 150 pounds. Thyroid was palpable but not felt to be enlarged. There was a grade II aortic systolic murmur which did not radiate into the neck. Liver edge was palpable just below the costal margin. Two-plus pitting edema of the ankles and calves was noted.

Laboratory data showed normal hemogram, urinalysis and chest roentgenogram. Liver function studies showed bromsulfalein retention of 13.5%, cephalin flocculation 4-plus in 48 hours, thymol turbidity 6 units, bilirubin 3.2 mg. per 100 ml.

Following admission he was treated for congestive heart failure with diuretics and digitalis, lost 16 pounds in 4 days and showed marked improvement of the dyspnea and orthopnea. He continued to manifest extreme weakness and tremulousness. Following complete disappearance of the edema, marked muscle wasting was noted. This was most pronounced in muscles of the pectoral group and in the interscapular area (see Fig. 1). Protein bound iodine studies were returned at this time and showed a level of 22 μg. per 100 ml. I_{131} uptake studies on two occasions were reported as 47% and 67% in 24 hours. He was given 6.4 millicuries of I_{131} followed by a course of propylthiouracil and later tapazole. The patient showed marked improvement several weeks following institution of therapy, gained 18 pounds of weight and was able to discontinue digitalis without recurrence of cardiac failure. There was marked increase in muscle mass and disappearance of the previously noted myopathy (see Fig. 2).

Fig. 1

Fig. 2

COMMENT. In this case, the classic signs of hyperthyroidism were missing and the patient presented with cardiac decompensation and severe myopathy. Following correct diagnosis and institution of therapy, there was marked improvement in both of these conditions. Lack of thyroid enlargement is again present here as is the usual evidence of hypermetabolism.

CASE 3. A 69-year-old woman was admitted to a general hospital in March, 1959, but required transfer to a mental institution because of psychotic behavior. History obtained from the family indicated that her behavior had become bizarre during the 4 preceding months. She had trouble with memory, became suspicious of persons around her, and was obsessed with religious activities. During periods of hyperactivity she would tear off her clothes and wreck her room. She also apparently had auditory hallucinations. Progressive muscular weakness became a noticeable feature of her illness, particularly in the last few weeks prior to admission. Past history revealed that she had had episodes of "nervousness" in the past, and had chorea at age 10. During her late teens she received iodine for thyroid trouble, but required no therapy since that time.

Physical examination revealed an agitated white woman who was in a delusional and hallucinatory state. There was muscle atrophy of the interscapular and marked weakness and atrophy of the quadriceps muscles bilaterally. Cardiovascular examination was normal. The thyroid gland was not palpable. Remainder of the physical examination was normal.

Laboratory data showed a normal hemogram, urinalysis, electrocardiogram and nonreactive serological test for syphilis. Although protein bound iodine and I_{131} uptake studies were not performed, an Achilles reflex test gave an abnormal value of 140 milliseconds with a sharp, narrow contraction phase.

Because of the psychotic behavior, hyperactivity, muscular atrophy and the abnormal kinemometric value, the patient was placed on propylthiouracil therapy. Response was detected after 2 weeks, and during the next 2 months marked improvement in the patient was noted. All psychotic manifestations disappeared, she gained a total of 16 pounds in weight with restoration of muscle mass and disappearance of the profound weakness. Repeat of the Achilles reflex showed an increase of the interval to a normal level of 200 milliseconds. The patient has continued to do well for the 6-month period following discharge.

COMMENT. Here the psychotic behavior of the patient dominated the clinical picture while the usual signs of hypermetabolism and glandular enlargement were again absent. As in the previous case, the marked muscle weakness and myopathy led to the suspicion of hyperthyroidism. Adequate therapy has returned the patient to normal activity.

Discussion. Atypical or unusual manifestations of hyperthyroidism have been described previously (Chapman and Maloof[3], Wohl and Shuman[11]). In most of these cases the more atypical manifestations were also present but were overshadowed by other findings which delayed recognition of the basic disease. In a far smaller group, few, if any, of the typical findings are present and proper diagnosis is suspected only by the realization that such symptoms can be produced by hyperthyroidism.

Manifestations of cardiovascular disease such as atrial fibrillation, angina pectoris, and cardiac decompensation are sometimes seen as the only symptoms in this condition, especially in older persons. Atrial fibrillation is probably the most common cardiac abnormality and was noted by Bortin, Silver and Yohalem in 8 of 50 cases with atrial fibrillation in a group of patients with no overt symptoms of hyperthyroidism[1]. It has been stated that the arrhythmia in such cases is less easily controlled with digitalis than in euthyroid patients with cardiac disease (Werner[10]). One of our cases responded rapidly to digitalis, causing us to think less seriously about hyperthyroidism initially. This has been the experience of others as well (Chapman and Maloof[3]). A large portion of hyperthyroid patients with cardiovascular

complaints have underlying heart disease although 15 to 20% show no cardiovascular abnormality following therapy.

Several myopathic syndromes have been described in association with hyperthyroidism, including chronic thyrotoxic myopathy as manifested by one of our cases, exophthalmic ophthalmoplegia (Werner[10]), myasthenia gravis (Wohl and Shuman[11]) and periodic paralysis (Overholt, Smith and White[9]). The latter two conditions have usually been seen as associated conditions in the presence of hyperthyroidism. Following adequate anti-thyroid therapy, severity of the myasthenia gravis may diminish, but use of Prostigmine is required even during the euthyroid state. Periodic paralysis has been noted in the presence of hyperthyroidism in several cases. Definite improvement is usually noted following appropriate therapy, and Hildebrand and Kepler have suggested that hyperthyroidism brings out a latent tendency toward periodic paralysis in affected individuals[6]. While weakness alone is the more common muscular complaint, severe muscle atrophy is also found and may be so extensive as to preclude walking in some cases. Dramatic improvement following institution of anti-thyroid therapy is usually observed.

Evidence of central nervous system involvement is also a frequent finding. Again, related symptoms may be so striking as to obviate diagnosis of the basic pathology. The degree of involvement may vary from increased emotional lability to encephalopathy with disorientation, delirium and occasionally convulsive seizures (Dewind, Commons and Starr[4]). It has been suggested that 20% of hyperthyroid patients manifest psychotic behavior, usually not severe enough to require hospitalization. Most cases manifesting severe nervous system involvement are characteristic of organic type disease. Bluestone, however, has reported 3 cases which presented as severe functional psychoses requiring hospitalization. Symptoms improved with therapy and did not recur[2]. This author suggests that the development of psychosis is dependent on the underlying personality structure and that the symptoms represent distortations of the prepsychotic personality. Significant improvement follows adequate therapy in such cases also, as shown by the last case.

Summary. Hyperthyroidism is not always an easily recognizable disease. This is especially true in older individuals. Typical symptoms of hypermetabolism and goiter may be partially masked by exaggeration of complaints referable to an organ system. In a few cases none of the classic symptoms may be apparent, and diagnosis results from the realization that the disease may present in any of several unusual forms. Three cases which stress this difficulty are presented.

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(Interlingua on page 230)

PROGRESS
OF
MEDICAL SCIENCE

OPHTHALMOLOGY

UNDER THE CHARGE OF

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RETINAL ARTERIAL AND ARTERIOLAR LESIONS ASSOCIATED WITH SYSTEMIC VASCULAR HYPERTENSION

A REVIEW OF SOME RECENT OPINIONS

BY HENRY P. WAGENER, M.D.

OPHTHALMOSCOPIC studies of normal and abnormal retinal vessels have been made ever since the invention of the ophthalmoscope over 100 years ago. The ophthalmoscopic characteristics of the changes which occur in the retinal arterial system in association with general systemic vascular disease and with hypertension have been recognized for at least 70 years, since their description by Gunn[16]. In most respects, Gunn's[16] description of these changes is still adequate. As Michaelson[29] expresses it, there has been a static ophthalmoscopic picture. However, to date, there has not been unanimous agreement on the mode of development of these lesions or on their significance with regard to generalized arteriosclerosis or systemic hypertension. There are a number of reasons for this lack of agreement among both opthalmologists and internists. Perhaps most important has been the indiscriminate use, especially by ophthalmologists, of the term "retinal arteriosclerosis" regardless of the size of the vessels involved and the changing concepts, especially among internists, of the nature and interrelationships of arteriosclerosis and hypertension.

THE SIZE OF THE RETINAL ARTERIAL VESSELS. Gunn[16] spoke of all the visible retinal arterial vessels as arteries. Some observers depend on histologic characteristics for the differentiation of arterioles from arteries. Thus, Friedenwald[14] stated that, "Since, by definition, arteries which do not possess an internal elastic lamella nor a continuous muscular coat are classified as arterioles, the whole retinal tree except for those branches in or close to the optic disc is arteriolar." A number of more recent authors Scheie[34], Wise[39], Snell[35] and Cogan[9] to name a few, accept the fact that most of the ophthalmoscopically visible retinal "arteries" are

really arterioles. Brust[5] thought that the vessels became arterioles after the second branching of the central retinal artery. Other observers tend to base the differentiation of arterioles from arteries on the size of the vessel. Thus I[37] wrote in 1958: "Kernohan[21] stated . . . that any arterial vessel less than 125 microns in diameter should be considered an arteriole. As *in vivo* measurements of the retinal arterial vessels just off the margin of the optic disc are said by several observers to range between 63 and 134 microns, it seems justifiable to regard the branches of the central artery as arterioles after they leave the optic disc." It would seem logical to assume then that it should be possible to observe in the retina "sclerotic" lesions of types that might affect arteries or arterioles, or both, but that most of the visible lesions would be classified as arteriolar.

TYPES OF ARTERIOSCLEROSIS. In discussing the question of the arterial changes occurring in persons with high blood pressure, Pickering[31] states: "Such a tendency to identify hypertension with structural disorders of the arteries produced the first great obstacle to understanding the part played by organic vascular changes in the natural history of maladies associated with raised arterial pressure. . . . The second great obstacle . . . is the term arteriosclerosis, which is so all-embracing that it means little more than non-inflammatory disease of the arteries." He adds that this term is applied not only to various diseases of the larger arteries but also to "the changes visible with the ophthalmoscope in tiny arteries, about 100 μ in diameter, in the retina; conditions which differ in almost every respect."

Pickering[31] lists under the heading of arterial lesions hypertrophy of the media (which occurs largely in association with hypertension), various degenerations of the media, and affections of the intima. Stating that atheroma is the chief condition which is included ordinarily in the term arteriosclerosis and that it affects and is almost confined to the intima, he adds that it is associated not infrequently with degenerative changes in the media and that this association is sometimes called "atherosclerosis."

According to Allen, Barker and Hines[2], arteriosclerosis obliterans is, from a pathologic standpoint, a manifestation of atherosclerosis or of a combination of atherosclerosis and medial arteriosclerosis in almost all cases. These authors state that arteriosclerosis is a term which has been used to include several different types of degenerative arteriopathy, among which is hypertensive arteriopathy, a widespread process involving primarily arterioles and small arteries and characterized by hypertrophy and thickening of the media. Both Pickering[31] and Imbriglia[20] called attention to the reduction of the ratio of the diameter of the lumen to the thickness of the wall demonstrated by Kernohan, Anderson and Keith[22] and by Morlock[30] in the arteries of various tissues of patients with hypertension, due chiefly to medial hypertrophy. A similar reduction of lumen to wall ratio was demonstrated in the arterial vessels of the choroid and retina by Manlove[28].

Imbriglia[20] noted that the lesions of essential hypertension are confined to the small arteries and arterioles of less than 100 microns in diameter. He stated: "Four main types of arteriolar lesions are noted in essential hypertension depending on the time of onset, duration and severity of the disease. These lesions can be classified in order of increasing severity as arteriolar spasm, arteriolar hypertrophy, arteriolar fibrosis, arteriolar necrosis." Pickering[31] states that medial fibrosis occurs

in small arteries and arterioles of the retina, brain and kidney in association with intimal proliferation and hyalinization. But he adds that two changes occur only in the small arteries and are particularly closely related to hypertension. These are arteriolosclerosis, the fatty hyaline intimal thickening characteristic of the benign phase of hypertension, and the acute fibrinoid arteriolar necrosis characteristic of the malignant phase. It is the consensus of contemporary opinion, he says, that arteriolosclerosis is the result of prolonged hypertension. Pickering[31] suggests that "acute fibrinoid arteriolar necrosis is a consequence of the intensity of the hypertension and of the speed with which it develops." But he states that all the other arterial lesions previously described, including fatty hyaline intimal thickening of the smallest arteries, "increase in frequency and severity with age, and, in this sense, may be regarded as ageing processes."

TYPES OF RETINAL "ARTERIOSCLEROSIS."

In the light of the character and distribution of the arterial and arteriolar lesions just described, it should be possible to observe in the retina evidences of atheroma, of atherosclerosis, of arteriolar constriction or hypertonus and of organic lesions of the arterioles associated with hypertension. It might be assumed that these conditions should be distinguishable ophthalmoscopically, but differentiation of organic lesions of the arterioles into medial hypertrophy, arteriolosclerosis, or arteriolar necrosis would probably require histologic examination.

Duke-Elder[12] states that localized atheromatous changes in the intima are not common in the retina. The site of election for such changes is in the central retinal artery within the optic nerve, particularly at the lamina cribrosa. Lesions which occur in the retina are outposts of this central process. Duke-Elder[12] gives as the ophthalmoscopic evidences of localized atheromas in the retina narrowing and irregularity of the lumens of the arteries, frequently most marked near the arterial divisions. Friedenwald[15] agreed with Duke-Elder's[12] statement with regard to the location of the atheromatous lesions. He wrote: "While the point of maximal predilection for atheroma in the retinal artery is at or behind the optic disc, small lesions of a similar type are not uncommon in the vessels that can be viewed with the ophthalmoscope." But he added, "It is only when an opaque spot in the vessel wall is seen associated with a localized constriction in caliber that one can assert with considerable confidence that a lesion is atherosclerotic not spastic." Scheie[34] agreed with Friedenwald's[15] views on the location and appearance of atheromatous plaques in the retina and added the suggestion that a plaque would cause a localized indentation of one wall of the arteriole rather than a waist-like constriction. Cogan[9] stated that there is abundant evidence in our histology that the retinal arteries develop atheromatous changes only in the immediate vicinity of the discs.

Leishman[27] stated that an atheromatous patch in a retinal arteriole is seen ophthalmoscopically as an opaque white mass which appears to erode or even obscure a portion of the blood column, or, in the case of a more extensive lesion, as pipe-stem sheathing of the arteriole. Contrary to the usual assumption that, in an atheroma, fibrosis is secondary to the lesion in the intima, the fibrosis is present first in Leishman's[27] opinion. The endothelial tube, the essential part of the artery, retains its resiliency although the outer wall has become rigid through fibrosis. If the volume of contained blood is reduced for a significant time, the en-

dothelium attempts to contain the diminished blood volume by partial retraction from the rigid outer wall. Cloudy swelling of the endothelial cells, deposition of fat and formation of new collagen fibers then ensue. The presence of atheromas, or their development, in the retinal arterioles might be explained on the basis of this reasoning. In Leishman's[27] words: "If this reasoning is correct, fibrotic rigidity of the outer wall of the vessel becomes the predisposing factor, and relative diminution of blood pressure and volume an exciting factor, in the production of the atheromatous lesion. Such a lesion, once established in a small vessel, will tend to shut off more distal portions of the vessel from the full systemic pressure and will allow a further 'seeding' of the atheromatous process in other fibrous portions in a distal direction."

Diffuse atherosclerosis presents in the retina a different picture from that characteristic of atheroma, which is termed intimal atherosclerosis by Scheie[34]. Duke-Elder[12] states that diffuse atherosclerosis (involutionary arteriosclerosis of Allbutt[1], medial arteriosclerosis) is an age change which is almost universal after the fifth or sixth decade. This senile change affects the retinal vessels diffusely, but it does not give rise to a markedly pathological clinical picture so long as the blood pressure remains within normal limits. Leishman[27] did not use the term "atherosclerosis," but he defined decrescent or involutionary sclerosis (which Allbutt[1] considered to be atherosclerosis) as an ageing process affecting arteries and arterioles and appearing histologically as a relative or replacement fibrosis of patchy distribution. It is present in almost all persons after the age of 60, but it may occur prematurely in younger individuals. Ophthalmoscopically, Leishman[27] says, the retinal arterioles appear diffusely straight and narrow with acute-angled branchings and diminished color of the blood columns, manifestations of lowered peripheral pressure resulting from relative rigidity of the larger arteries. Most authors agree with this description of senile retinal arterioles; some think that the narrowing of the arterioles is secondary to the presence of an atheromatous plaque in the central retinal artery. It is questionable whether purely ageing changes will cause a decrease in the transparency of the arteriolar wall as suggested by Duke-Elder[12].

RETINAL ARTERIOLAR CHANGES ASSOCIATED WITH SYSTEMIC HYPERTENSION. Most observers agree that diffuse, generalized, uniform narrowing of the arterioles in a youthful retina (so-called young retinal arterioles) is indicative of constriction or hypertonus of the arterioles, is significant of elevation of blood pressure and is reversible if the blood pressure returns to normotensive levels. Thus, Duke-Elder[12] states that narrowing and straightening of the arteries is the most constant and characteristic sign of increased tension. Defining tonus as "a sustained physiologic contraction . . . not to be confused with spasm which implies a sudden violent contraction of limited duration," Leishman[27] stated that, when the blood pressure rises, young retinal arterioles become narrow, straight, paler than normal and have acute-angled branchings indicative of diffuse hypertonus in a vessel with normal walls. He considers diffuse hypertonus to be the characteristic sign in the retinal arterioles of systemic hypertension.

There is no such general agreement on the nature or significance of localized narrowings in the retinal arterioles which are variously considered to be focal areas of sclerosis, of "spasm," of constriction, or of hypertonus. After a rather extensive survey of the problem

in 1958, I[37] reached the following conclusions: "There seems to be adequate proof also, both clinical and experimental, that generalized and focal narrowings of small arteries and arterioles in the brain and in the retina can occur as functional manifestations in persons with blood pressures elevated by any of several causes. It was thought originally that all such focal narrowings were organic. It seems obvious now, however, that although some of the localized narrowings undoubtedly are due to organic sclerosis, either primary atherosclerosis or arteriolar sclerosis (which probably is secondary to preceding functional contraction), others are fundamentally functional, whether exclusively so or superimposed on a previous sclerotic lesion. It is not always possible to determine at a glance whether a particular narrowed zone represents functional contraction or sclerotic thickening of the vessel wall. However, symmetrical (waistlike) narrowings should be regarded as functional until proved otherwise. If careful examinations are made at intervals over an extended period, it can be seen that functional focal narrowings vary in number and severity and in some cases even disappear with time. . . . Increase and decrease in their number and severity follow rather closely the rises and falls in the systemic blood pressure, not only in cases of acutely rising blood pressure, as with toxemia of pregnancy, but also in chronic progressive essential hypertension." No doubt I should have written atheroma or intimal atherosclerosis instead of primary atherosclerosis. In an addendum, I[37] stated that Leishman[27] interpreted some of the local narrowings in the retinal arterioles as segments of hypertonus and others as segments of hyperplasia of the vessel wall. It is possible that cinematography of the retinal vessels, developed by Swan and Bailey[36], may in the future permit more accurate or earlier differentiation between functional and organic lesions in the retinal arteries and arterioles.

ORGANIC CHANGES IN THE RETINAL ARTERIOLES IN ASSOCIATION WITH SYSTEMIC HYPERTENSION. Most authorities are of the opinion that persistent systemic hypertension can cause the development of organic wall changes in previously normal retinal arterioles. In discussing the mode of development of hypertension (hyperpiesis), Doggart[11] speaks of initial angiospasm which tends to induce generalized arteriolar sclerosis. In his opinion, "So far as the *retinal arteries* are concerned, the usual sequence of disorder consists of (a) spasm, (b) sclerosis, (c) constriction of the lumen and (d) obliteration." He adds that spasm as a precursor of arteriosclerotic changes is transient usually and that sustained reduction in the caliber of the retinal arteries almost invariably means encroachment upon the lumen by intimal proliferation.

Change in the color of the arteriole to the so-called copper-wire or silver-wire appearance and alterations in the appearance or course of the vein or venule at the point or points where the arteriole crosses it, signs described originally by Gunn[16], are still the most easily recognized and the most dependable signs of organic change in the wall of the arteriole; they are produced by thickening and loss of translucency or transparency of the wall. These ophthalmoscopic appearances were presumed by Gunn[16] to be due to hyaline degeneration of the arterial wall induced by increased arterial tension. In a later paper, Gunn[17] stated that old age did not produce these changes, but he did not state clearly that they were caused always by increased arterial tension.

The lesion producing these characteristic ophthalmoscopic signs in the

retinal arterioles is termed arteriolar sclerosis or arteriolosclerosis by probably the majority of recent authors, at least in the United States. Duke-Elder[12] uses, apparently as an equivalent designation, the term "diffuse hyperplastic arteriosclerosis." He adds to the characteristic signs previously mentioned marked localized differences in caliber and irregular tortuosity and sheathing of the larger arteries and increased visibility and corkscrew tortuosity of the arterioles around the macula, changes which are stressed by other authors also, but probably are not as easily assessed as are color changes and arteriolovenous crossing phenomena. Leishman[27] defines arteriosclerosis as a diffuse hardening or stiffening of the arteries, due most commonly to high blood pressure. The initial response is physiologic hypertonus; this is followed by hypertrophy and hyperplasia of the intima and, if time is allowed, by replacement fibrosis. These changes were considered to be of a reactive nature and hence Leishman[27] used the term "reactive sclerosis" to designate the organic wall changes produced in the retinal arterioles by persistent, but not fulminating, hypertension.

Whether or not the ophthalmoscopic signs of retinal arteriolosclerosis are to be interpreted as always indicative of hypertension is debatable. Some authors and observers think that they should be. For example, Scheie[34] wrote: "The changes of arteriolar sclerosis, on the other hand, furnish an estimate of the damage to the arterioles due to the wear and tear of elevated intra-arterial pressure." And Bedell[4] said that typical copper-wire and silver-wire arteries are distinctively hypertensive. Salus[32] agreed practically, with a few reservations based largely on certain, some relatively minor, variations in ophthalmoscopic appearances which are sometimes difficult to interpret. He pointed out that periarterial wall opacification should not be termed silver-wire and that tortuosity of the retinal vessels is an equivocal sign and should be used only with great caution in the ophthalmoscopic diagnosis of hypertension and arteriosclerosis. According to Salus[32], the "nicking sign" (in which the vein is slightly indented by the crossing artery but the nick or arch just corresponds to the width of the crossing artery) is diagnostic of arteriosclerosis but may or may not be associated with high blood pressure. On the other hand, the "arching sign" (in which the vein is attenuated for several arterial widths on either side of the artery which crosses it, alters its course in the arch and may be invisible in the center of the arch) is always diagnostic of established high blood pressure. Biro[6] called attention to the so-called "reversed" crossing phenomena which develop when the vein crosses over the artery instead of under it. He described variations from the normal appearance of the overlying vein produced by sclerosis of the underlying arteriole. He stated that such changes in the vein are seen only in association with high blood pressure and that, though they do not play a part in causing branch vein thrombosis, they always indicate a fixed hypertension of high grade. In a later paper, Biro[7] described the vessel changes he observed in 831 young persons with hypertension of varying degrees of severity. These cases were found among a group of 10,000 athletes between the ages of 15 and 30. He thought that the earliest visible change was a broadening of the reflex stripe which he attributed to an optical change in the vessel wall caused by the increased tension and not to organic sclerosis as it disappeared when the blood pressure returned to normal levels. Definite narrowing and sclerosis of the retinal arteries was seen in the

more advanced cases with higher blood pressures.

Other observers, Ballantyne[3], for instance, contend that, although the characteristic ophthalmoscopic signs of retinal arteriolosclerosis are always intensified when the blood pressure is elevated, these signs can be present in individuals with normal pressures. Thus, Sauter[33] spoke of a simple or pure arteriosclerotic fundus not associated with hypertensive, diabetic or similar fundus changes and stated that retinal arteriolosclerosis is caused by hypertension or age, or both. Behrendt[5] stated: "I was not able to find a clear-cut relation of any of the crossing phenomena to hypertension itself. On the contrary, I found many cases of small or no changes of the crossings or even of the fundus in patients with long and well-corroborated histories of hypertension. . . . On the other hand, I was able to find cases of well-marked crossing phenomena in normotensives or even in persons with a long history of hypotension. . . . This seems to indicate that hypertension by itself is not the cause of the changes at the crossings. On the contrary, it seems that some vascular process is involved which can be precipitated by hypertension but may also appear under other circumstances."

Davis and Landau[10] studied the vessels in the retina and in the conjunctiva of 80 patients, between 45 and 89 years of age, with arteriosclerosis and characteristic arteriosclerotic complications in heart, brain or extremities but without hypertension, the diastolic pressures being below 90 mm. Hg in all cases. They stated that 57 of the 80 cases had arteriosclerotic fundi according to Leishman's[27] criteria; in 20, signs of both arteriosclerosis and hypertension were present in the fundi; 1 had a hypertensive fundus; and 2 had normal fundi. This would seem to indicate that ophthalmoscopic appearances presumedly characteristic of hypertension were present in a fourth of their cases in the absence of systemic hypertension. It is of interest, also, that some observers, among them White and Waskow[38], Wise[40], Heinsius[19] and Larsen[25,26], have noted retinal arteriosclerosis in young diabetics without hypertension or diabetic retinopathy. Larsen[25] wrote: "In my study, I found retinal arteriosclerosis to be a very characteristic lesion in long-standing juvenile and middle-aged diabetes. Ophthalmoscopically, the arterial changes resemble those "copper-wire" arteries, "silver-wire" arteries and arteriovenous crossing phenomena seen in old, arteriosclerotic patients, but differ by being much more severe in these diabetics than in non-diabetics of the same age. Arterial occlusions with new channel formation are not seldom observed." In a personal communication, Larsen[26] indicated that such ophthalmoscopic appearances could be seen in patients without systemic hypertension. Apparently, he considers these arteriosclerotic changes to be non-hypertensive since, in his text, he states that hypertensive changes in the retinal vessels do not differ from those seen in non-diabetics. It may be of some importance in terminology and diagnosis to take into account the fact that most of these "arteriosclerotic" changes in the retinal arterioles are seen in association with diabetic retinopathy.

Writing on the question whether malignant hypertension and benign hypertension are different diseases, Hafkenschiel[18] expressed the opinion that the same pathogenetic mechanism is at work in both the malignant and the benign disease states. He added, "The important therapeutic conclusion is that blood pressure reduction seems to be reasonably well established as the one important factor in arresting vascular

deterioration." In their studies of a group of 44 patients, aged 30 through 69, with primary hypertension, Kirkendall and Armstrong[23] made some interesting observations. They considered the arteriolosclerotic changes and the hypertensive changes separately after the method of Scheie[34]. They recognized as evidences of arteriolosclerosis, copper-colored and silver-colored arterioles, arteriolovenous crossing phenomena and, ultimately, arterial and venous obliteration. Hypertensive (angiospastic) changes, they thought, were indicated by generalized and focal narrowing of the arterioles and, in cases with more severe arteriolar lesions, by hemorrhages, exudates and papilledema. They found that generalized and localized areas of active constriction could be relaxed by effective therapy. But they noted persistence or progression of localized constrictions secondary to arteriolosclerotic changes, even if the blood pressure was lowered. They concluded: "Whether blood pressure is lowered or not, arteriolosclerotic changes continue to appear in the optic fundi. Changes for the worse occur in arteriolar thickening (and probably tortuosity), arteriolar venular crossing phenomena and atherosclerotic plaques. This progression may be caused by the closing off of vessels from lowered arteriolar blood pressure or to extension of changes in the endothelium which originally narrowed them. . . . The progression of sclerosing lesions in arterioles in patients with adequate blood pressure reduction emphasizes a defect in current methods of treatment." These observations, if accurate, lend some support to the concept that arteriolosclerosis may develop independently of elevated blood pressure. In commenting on Kirkendall and Armstrong's[23] article, Klien[24] wrote, "It is unfortunate that no mention was made of the hemodynamic disturbances from too sudden therapeutic reduction of blood pressure, which may play a role in the pathogenesis of occlusion of the central vein (stagnation thrombosis). This chapter would have been a good medium for spreading this practical knowledge."

CLINICAL RETINAL PATTERNS OF SYSTEMIC HYPERTENSION. In his article "Error and Discovery in Fundus Diseases," Michaelson[29] stated that understanding of fundal diseases requires a knowledge of the clinical pattern (establishment of the static ophthalmoscopic picture), discovery by ophthalmoscopy of the initial lesions from which the clinical pattern evolved, determination of the events leading up to the initial lesions and, finally, ascertainment of the proper treatment of these events. The static ophthalmoscopic picture of the retinal arterial lesions of hypertension consisted, according to Michaelson[29], of narrowing of the vessels due to angiospasm or hypertonus of the vessel walls, caliber variations due usually to local hyperplasia of the vessel wall, changes at the arteriovenous crossings due to hyperplasia of the vessel walls and lack of retinal transparency, and fullness of the vessels due to increased diastolic pressure. Granting that the ophthalmoscopic signs listed by Michaelson have been accepted as evidences of vascular damage without the addition of any practical suggestions for more refined diagnosis and hence their ophthalmoscopic pattern may be termed static, the interpretation of their significance in regard to systemic hypertension has not been uniform and unchanging. There are, in the United States at least, two rather basically distinct schools of thought represented, for example, by the opinions of Elwyn[13] and Scheie[34] expressed in publications in 1953.

In Elwyn's[13] opinion, arteriosclerosis is one and the same disease whether

the intima presents an atheroma, a localized fibrous thickening or a hyaline thickening of the arterioles. He thinks that the changes due to aging of the arteries must be separated from the changes which constitute arteriosclerosis proper. Aging manifests itself in dilatation and tortuosity of the arteries. When the irregular and patchy changes of arteriosclerosis are added, they produce an irregularity in the appearance of the blood column. There will be angular tortuosity of the vessel wall, localized variations in caliber of the arteries, localized arteriovenous constriction and widening of the arterial light reflex. These signs, he states, will become noticeable ordinarily only in the sixth decade and beyond. The presence of signs of retinal arteriosclerosis in young or middle-aged persons suggests persistent arterial hypertension but the signs are not the signs of general arterial hypertension but of aging and arteriosclerosis. In the early stages of essential hypertension, and sometimes even in advanced stages, there are, according to Elwyn[13], no changes in the retinal vessels to indicate premature aging or arteriosclerosis. In long-standing cases of hypertension, signs of aging and sclerosis may appear and some of the arteries assume a copper-wire or silver-wire appearance indicative of arteriolosclerosis. Elwyn[13] states in another chapter that spastic contraction of the retinal arteries occurs in certain cases of hypertension and involves all the arteries. The narrowing produced is noticeable particularly in the secondary branches. This spastic contraction may be present alone or may be superimposed on pre-existing arteriosclerosis. Unless it is added to previously present arteriosclerosis, spastic contraction appears as a thinning of the artery throughout its extent, without irregularity, so that the smaller and more peripheral branches almost or actually disappear from view. Histologically, the arteriosclerotic changes in the ophthalmoscopically visible branches of the central retinal artery are atheromatous in type. According to Elwyn[13], "In the smallest arteries and arterioles, which have no elastic fibers and are not visible ophthalmoscopically, the aforementioned arteriosclerotic process does not take place. Here there are found hyalinization and lipoid deposits such as may be present in the arterioles and prearterioles of organs like the spleen, kidneys, pancreas, and brain. This "arteriolosclerosis" of the retinal arteries occurs in combination with arteriosclerosis of the central artery and its branches under certain conditions which will be discussed later. . . . In the retina the hyaline and lipoid deposits in the arterioles and prearterioles occur in association with arteriospastic retinitis."

Unlike Elwyn[13], Scheie[34] thought of the whole retinal arterial tree as arteriolar in nature except for the central artery and possibly some of its large branches near the disk. In his opinion, intimal atherosclerosis and arteriolar sclerosis, which are the most common types of arterial disease seen in the retinal vessels and which are confused frequently in ophthalmologic literature, should be differentiated carefully because of their different nature and significance. Scheie[34] stated that, if hypertension, even of mild degree, continues for a sufficiently long period, the changes of arteriolar sclerosis will develop in the retina and will be recognized ophthalmoscopically by widening of the arteriolar light streak, by a copper-wire or silver-wire appearance of the arterioles and by arteriolovenular crossing changes, such as indentation, tapering, banking, and deflection of the vein. Like Elwyn[13], Scheie[34] recognized generalized narrowing or atten-

uation of the retinal arterioles as the primary or most distinctive evidence of elevation of blood pressure. But Scheie[34] thought, additionally, that, "In severer hypertensive states irregularities in the caliber of blood vessels, thought to be due to localized spasm and contraction of the wall of the arteriole, may be superimposed upon generalized narrowing. The narrowing and irregularity may increase until the vessels become thread-like."

Leishman[27] applied the interesting concept of "defense by sclerosis" to the problem of determining the significance of retinal arteriolar lesions in the diagnosis and prognosis of systemic hypertension. He wrote: "This concept of defense by sclerosis is conceived in the limited sense that the reactive changes induced in a vessel wall as a result of hypertension appear to protect the wall from the more severe acute degenerative lesions of high blood pressure. Sclerosis may not only protect the wall from necrosis, but, also, may in some cases predetermine, and in others modify, the whole course of the hypertensive disorder." Leishman[27] thought that, if hypertension occurs in a person whose vessels are significantly affected by involutionary sclerosis, he will be protected from serious elevations of diastolic pressure in proportion to the degree and extent of his sclerosis, because of the reduced areas capable of effective hypertonus or diffuse active constriction. When, or if, the blood pressure rises, only those portions of senile arterioles will become hypertonic which are not fibrosed and which are still contractile. Other portions will dilate passively. If the whole vessel is involved by fibrosis, it will dilate throughout its length. Then, even if the hypertension is severe, senile ("old") retinal arterioles will be larger and wider than normal. Young retinal arterioles, on the contrary, will react to hypertension by diffuse hypertonus (contraction, narrowing) throughout their length. Histologically, "old" vessels will have normal walls in the hypertonic segments and thinner than normal walls in the dilated segments with more collagen and fewer nuclei than normal; diffusely hypertonic "young" arterioles will have normal walls. Involutionary sclerosis is normal in old age but may occur prematurely in arterioles as well as in the larger arteries. For this reason, Leishman[27] bases his decision as to whether he is dealing with "old" or "young" arterioles on the age characteristics of the fundus as a whole. "Old" arterioles are found in a senile appearing fundus, in which the optic disk is pale and slightly hollow, the ocular media are hazy, the retinal reflexes are diminished so that the retina appears dull, there is some disturbance of retinal pigmentation and colloid bodies are present. "Young" retinal arterioles are found in a youthful appearing fundus, in which the media are clear, the retinal reflex is brilliant, the disk is of a healthy pink color, retinal pigmentation is uniform and no colloid bodies are seen.

Leishman[27] expressed the opinion that it seems to be assumed by most authors that the arterioles are universally capable of diffuse increase in tonus, and that the possibility that arteriosclerosis may play a part in modifying the course of hypertension appears to have been disregarded. The normal aging processes in the walls of arteries are either omitted or dismissed too lightly in most discussions of arteriosclerosis. A few cases of primary essential hypertension, Leishman[27] said, run a fulminating course; the remainder constitute the group of so-called benign essential hypertension. Individual cases in this group will show great variations in course and severity. The difficulty in classifying these cases is

due to the failure to appreciate the importance of the arteriosclerotic factor.

According to Leishman[27], cases of involutionary sclerosis with hypertension will be found to make up the largest group and cases of severe hypertension with reactive sclerosis the next largest group among patients with primary hypertension. He wrote: "These groups are regarded by physicians as a single homogeneous group (benign essential hypertension), in which the conditions have a common pathological basis and differ only in respect to the severity of the illness. This conception is not borne out in the present studies, since the groups present entirely different ophthalmoscopic features and the histological evidence suggests fundamental differences in pathogenesis."

Leishman[27] described five different types of ocular fundi encountered in patients with primary hypertension, two in persons with pre-existing involutionary sclerosis and three in persons with normal youthful arteries and arterioles. In his Group 2, "Involutionary Sclerosis with Hypertension," the senile arterioles show irregularly distributed widened segments in which, because of fibrosis, passive dilatation occurs while the rest of the vessel remains narrowed because of hypertonus. In Group 3, "Advanced Involutionary Sclerosis with Hypertension," because of diffuse fibrosis in all the main branches, the main arterioles are red, wide and tortuous against a senile fundus background and the secondary and tertiary branches are straight and narrow. In Group 5, "Early Hypertension in Youthful Vessels," the arterioles are diffusely constricted, straight and narrow against a youthful fundus background. In Group 6, "Fulminating Hypertension," the arterioles are diffusely narrowed and pale and show segments of accentuated pallor with further reduction and fine variations of caliber. The arteries near the disk, however, may approximate normal caliber. An arteriole may be thrombosed and later reduced to a residual white thread due to focal necrosis of the arteriole. Arteriovenous crossing changes are seen. Retinopathy with papilledema is present usually when the patient is first observed. In Group 7, "Severe Hypertension with Reactive Sclerosis," a severe hypertensive stimulus in youthful vessels has resulted in reactive changes progressing from hypertonus through hyperplasia to replacement fibrosis. The retinal arterioles are tortuous. There are arteriovenous crossing phenomena. The small arterioles and the distal parts of the larger ones are straight and narrow indicating hypertonus. Portions of the arterioles are pale, with increased visibility of the walls and fine irregularity indicating hyperplasia and other portions are full and red indicating fibrosis. Thus signs of hypertonus, of hyperplasia and of fibrosis may be seen concurrently in different portions of a single arteriole and its branches. Leishman[27] thought that the majority of middle-aged patients with hypertension would be found to belong to this group though in the end stage of the process, he said, it might not be possible to distinguish the arteriolar lesions of Group 7 from those of Group 3. He expressed the opinion that, "The ophthalmoscopic interpretations derived from these studies and stated in terms of physiology and pathology, appear to have some meaning with regard to the assessment of the general medical condition of the patient."

As Michaelson[29] saw it, Leishman's[27] basic thesis was that hypertonus is a measure not only of the hypertensive process but also of the capacity of the vessel wall to respond to that process.

this capacity being dependent on the age of the patient and the presence or absence of accompanying involutionary sclerosis. Leishman[27] was the first, Michaelson[29] thought, to supply the second requisite for the understanding of the ophthalmoscopic picture of hypertension, ophthalmoscopic discovery of the initial lesion. It was shown that the initial lesion consists not only of the action of the hypertonic factor on the vessel wall, but also of the capacity of the vessel to react, which depends on the degree of sclerosis of the vessel wall. Although not fully in agreement with Leishman's[27] view that, in association with systemic hypertension, dilatation of the retinal arterioles was always preceded by a stage of narrowing, Michaelson[29] was convinced that he and his associates had made fewer mistakes in diagnosis and prognosis since accepting the essential truth of Leishman's[27] observations. It would seem that properly controlled studies by internists and by other ophthalmologists are indicated to test the validity of Leishman's[27] observations and conclusions.

Summary. It does not seem possible at present to state categorically whether or not the ophthalmoscopic signs thought to be diagnostic of retinal arteriolosclerosis can be produced by processes other than established systemic hypertension. Determination of the significance of various ophthalmoscopically visible abnormalities in the retinal arteries and arterioles might be made more definite if ophthalmologists would abandon the general term "retinal arteriosclerosis" and state, as accurately as possible, whether the lesions they describe and photograph are atheromas, or atheromatous plaques, diffuse atherosclerosis or arteriolosclerosis.

Leishman[27] has introduced an interesting new system of classifying hypertensive retinal lesions from the standpoint of diagnosis and prognosis of the systemic disease. His system is based primarily on the concept of defense by arteriosclerosis and of the resultant difference in severity and course of the hypertension dependent on whether or not the elevation of blood pressure develops in individuals with pre-existing diffuse atherosclerosis (involutionary sclerosis). Ophthalmoscopic examination of the ocular fundi will aid in the differentiation of the types of vascular systems on which the hypertension is implanted since it permits ready recognition of old as opposed to youthful arteries and arterioles regardless of the actual age of the patient.

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SURGERY

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THE INTESTINAL PHASE OF GASTRIC SECRETION*

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I. The Intestinal Stimulus. HISTORY. Pavlov, writing in 1902[59], described studies in which the secretion of gastric acid was stimulated by the introduction of food into the small bowel. He failed to mention the intestine, however, in his final statement concerning factors exciting gastric secretion. Although this phenomenon was confirmed by other groups[9,33,46,50,68], little attention was paid to it, however, until 1925, when Ivy, Lim and McCarthy[40] demonstrated beyond dispute that the intestine, upon instillation of food, did initiate the production of acid by the stomach.

MODE OF PRODUCTION. The classic experiments for the demonstration of the intestinal phase of gastric secretion[40] utilized dogs with a total denervated gastric pouch and esophagoduodenostomy. These animals secreted acid following a mixed meal with a latent period of one to 3 hours. Raw meat itself did not provoke gastric secretion, and it was felt that this material traversed the gastrointestinal tract too rapidly. If raw meat juice, however, was given by mouth there was acid secretion after a 1 to 2 hour delay. Hydrochloric acid in 0.2% and 0.4% concentration inhibited the production of gastric acid if swallowed, but stimulated acid secretion if placed into the small bowel distal to the ampulla of Vater. Milk by mouth caused a flow of gastric juice which was enhanced if the milk was predigested with pepsin or pancreatin. Ivy, Lim and McCarthy[40] found that histamine, beta-alanine, hypertonic salt solution and saponin all stimulated the flow

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of gastric juice, while adrenalin, starch, glucose, water, fat, and atropine inhibited it. This study was confirmed by Webster and Armour[70] who noted the effect of instillation of food into the small intestine distal to the obstructed pylorus of the dog. They also found a latent period of one to 3 hours, and confirmed the inhibitory effect of fat and atropine. They observed that dogs whose nutrition was maintained for long periods by pure intestinal feeding lost all appetite, and concluded that the gastric secretion occurring in their experiments was the expression of a pure intestinal phase. Ivy and McIlvain[42] prepared dogs with blind fistulae of the distal duodenum and proximal jejunum into which they introduced various test substances to study their effect upon gastric secretion. Eightieth normal to N/10 hydrochloric acid, N/10 to N/2 butyric acid, N/20 hydrochloric acid in olive oil, 10% magnesium sulfate, 10% NaCl, dog gastric juice, 10% glycerine, 7% Armour's meat extract, ethyl alcohol, or 10% Witte's peptone stimulated the production of acid when placed into the fistula. On the other hand, fresh meat juice, ground meat, olive oil, sodium carbonate solution, ammonium hydroxide, distilled water, or physiologic saline failed to produce gastric secretion. Other means of provoking the intestinal phase include small bowel distention[56, 66] perfusion with intestinal chyme, and the instillation of acetylcholine[66].

NATURE OF AGENT. The method by which the intestine stimulates gastric secretion was long in doubt. Initially it was suggested that this is mediated by a nervous reflex, but in 1941, Gregory and Ivy[31] demonstrated that a completely denervated pouch of gastric mucosa transplanted to the subcutaneous tissue secretes acid when food is introduced into the small intestine. Since this demonstration of the humoral nature of the intestinal stimulus, there has been much speculation as to the agent's identity. Some suggested that this stimulation is due to a gastrin-like material[3,18,42] while others held secretagogues absorbed from food[3,19,37] to be the responsible substances.

Sircus[66] studied this problem in dogs with Heidenhain pouches and with isolated loops of small intestine, either jejunal or duodeno-jejunal. He placed a balloon in the small bowel loop and distended it for more than 30 minutes at 15 to 30 mm. Hg pressure. Free acid was produced from the Heidenhain pouch and no difference in response between the pure jejunal loops and the duodeno-jejunal loops was noted. There was no relation between the distending pressure and the magnitude of the response. Procaine applied locally to the small bowel mucosa abolished the gastric secretion caused by distention of the loop. He was also able to stimulate gastric secretion by perfusing the small bowel loops with intestinal chyme, 1% acetylcholine, or 0.4% hydrochloric acid. Sircus concluded that the intestinal stimulus to gastric secretion that he provoked was certainly humoral because the Heidenhain pouch was completely denervated. He felt that this humoral agent is a hormone and not a secretagogue since he was able to stimulate the pouch by distention and by dilute hydrochloric acid. Moreover, he was able to block all stimuli with the local application of procaine, suggesting that the hormone is liberated by local reflex. He noted similarities to the activation of the gastrin mechanism, but could not say that this material is gastrin. Nagano *et al.*[56] confirmed this work and likewise noted that the factors affecting the release of the intestinal phase stimulus were similar to those which produced gastrin from the antrum.

Because of the well known gastric secretory activity of histamine, many investigators have speculated about its relation to the intestinal phase stimulus. Histamine is known to be present in large amounts in the portal vein blood of normal animals[2], it is known to have an increased concentration in the urine following a meat meal[37,69], and meat is known to be a strong stimulus of the intestinal phase. Irvine *et al.*[39] have suggested that histamine is liberated from meat by the decarboxylation of l-histidine by intestinal bacteria. They found that in humans and in dogs the increase in free histamine in the urine following a meat meal is similar and equal to that following the administration of an equivalent amount of l-histidine by mouth. Reducing the gastrointestinal flora with succinylsulfathiazole decreased the amount of urinary histamine following the meat meal or the ingestion of l-histidine by mouth. Irvine and Code[37] studied the temporal relationship between the rise in urinary concentration of histamine and the increase in gastric acid output following the ingestion of a meat meal by mouth or the introduction of meat into the jejunum in an animal with a ligated pylorus. They concluded that the increase in urinary histamine depended upon meat, but they found no relationship between the increase of acid from the pouch and the urinary histamine, and suggested that histamine liberated into the portal vein might be removed or destroyed by the liver.

RELATION TO OTHER PHASES OF GASTRIC SECRETION. The relation between the intestinal and cephalic phases of gastric secretion has been little studied. Gregory and Tracy[32] reported that in antrectomized dogs with a denervated fundic pouch (that is, intestinal phase preparation) the output of acid following histamine stimulation was slightly potentiated by urecholine and greatly increased by carbachol, both cholinergic drugs. They repeated this experiment in dogs with antrectomized, total gastric pouches and obtained similar results. On the other hand, Lester Dragstedt, II *et al.*[22] studied the effect of transthoracic vagotomy on Heidenhain pouch, antrectomized dogs and noted increased acid output of the pouch following vagotomy. This stimulation of the intestinal phase following vagotomy was attributed to the loss of duodenal inhibition, that is, the diminished acid produced in the main stomach caused less duodenal acidity with the consequent increase in Heidenhain pouch output. Vagotomy was also found to prolong the period of acid secretion by the Heidenhain pouch in the antrectomized dog fed a meat meal. Dragstedt, Sr.[19] speculated that the intestinal phase may be important in individuals with inadequate cephalic or antral phases in whom food is not sufficiently acidified in the stomach to evoke duodenal inhibition.

The relation between the antral and intestinal phases of gastric secretion was studied by Woodward *et al.*[72], who prepared animals with Heidenhain and isolated antral pouches. They found that irrigation of these isolated antra with N/10 hydrochloric acid did not stop the gastric acid output from the Heidenhain pouch stimulated by the intestinal phase. Margolus and Harrison[51], using a similar preparation, found that irrigation of the isolated antrum with N/10 hydrochloric acid profoundly diminished the acid output of the Heidenhain pouch (intestinal phase stimulus). Woodward *et al.*[73] repeated this work and again found no inhibition of the intestinal phase when the *denervated* isolated antral pouch was irrigated with hydrochloric acid. When, however, they irrigated an isolated antral pouch to which the innervation had

been preserved, a decrease in Heidenhain pouch output following acid irrigation of the antrum was recognized. No explanation for the significance of the preservation of the innervation of the antrum was advanced.

INHIBITION OF THE INTESTINAL STIMULUS. Atropine has been shown profoundly to inhibit the intestinal phase of gastric secretion[40,70]. Nagano *et al.*[56] stimulated the intestinal phase by distending the duodenum and found they could inhibit the resultant output of acid by the administration of phenergan or secretin given intravenously and by the duodenal instillation of N/10 hydrochloric acid.

II. Intestinal Inhibition of Gastric Secretion. Inhibition of gastric secretion by the duodenum was first noted by Shemiakin[64] and confirmed by Sokolov[68]. It is initiated by hydrochloric acid, fat, and various carbohydrates.

ACID IN THE DUODENUM. Sokolov's[68] observation of the inhibitory effect on gastric secretion of acid in the duodenum has been widely confirmed[15,17,18,43,55,60,67]. Pincus *et al.*[60] demonstrated that the inhibition of gastric acid did not occur until the duodenal pH was 2.5 or lower. This was substantiated by Jones and Harkins[43]. Brackney *et al.*[6] verified this duodenal inhibition in studies on Heidenhain pouch dogs divided into two groups. In half the animals resection was performed from a point 2 cm. distal to the pylorus through the proximal jejunum, while in the remaining animals this same area was transplanted into the mid-portion of the small bowel. They found increased hydrochloric acid secretion in all animals, 84% to 820% in the resected group, and 113% to 364% in the transplanted group. They attributed this increase to the removal of duodenal inhibition. Similar findings were reported by Andersson *et al.*[1] who studied the secretory response to exclusion of the antrum and duodenum with later antral resection leaving the duodenum excluded. Woodward *et al.*[72] isolated a segment of the duodenum distal to the pancreatic duct in animals with Heidenhain pouches reporting that acid irrigation of this isolated segment of bowel did not decrease gastric secretion, contrary to the findings of Pincus *et al.*[60]. However, since they did not irrigate the proximal duodenum with acid as Pincus did, the results are not comparable. Day and Komarov[17] noted that instillation of acid into the duodenum inhibited all three phases of gastric secretion, but did not inhibit acid output stimulated by histamine. Recent studies[15,67], however, would indicate that even this stimulus could be inhibited in innervated gastric pouches following instillation of hydrochloric acid, glucose, hypertonic salt, or peptone into the duodenum. Acidification of the duodenum has also been shown to inhibit gastric motility[29,62].

The mechanism of duodenal inhibition of gastric secretion is unknown. Dragstedt[18] has suggested that acid in the duodenum inhibits the release of gastrin from the antrum. Most experimental work concerning the mechanism of duodenal inhibition has centered on the importance of vagal innervation. Code and Watkinson[15] prepared two groups of animals with fundic pouches, some innervated and some denervated. They inserted duodenal cannulae into these animals, irrigated the duodenum with hydrochloric acid following meat meals, and were able to secure inhibition of gastric secretion only in those animals with an innervated gastric pouch. Gregory[29], however, studied animals with completely denervated transplanted gastric pouches in whom acid production was stimulated with subcutaneous histamine. He was able to inhibit motility uniformly and to inhibit acid secretion sporadically by the

instillation of olive oil, hypertonic glucose, N/10 hydrochloric acid or sodium oleate solution into the duodenum. He felt that this inhibition was due to a humoral agent of duodenal origin. Sircus[67], on the other hand, was regularly able to inhibit acid production by irrigating the duodenum with hydrochloric acid in Pavlov pouch animals, but was unable to inhibit acid production with regularity in Heidenhain pouch animals. He concluded that gastric inhibition following instillation of acid into the duodenum depended upon the nervous connection between the duodenum and the gastric pouch.

This problem was further studied by Jones and Harkins[43] in Pavlov pouch and Heidenhain pouch dogs. In their preparation, the duodenum was intermittently isolated from the rest of the gut by placing a lucite valve or a balloon in the distal end of the duodenal segment. They gave the animal a test meal of 100 ml. of 10% ethyl alcohol and 5 minutes later perfused the duodenum with either N/10 hydrochloric acid, N/10 sodium bicarbonate, or physiologic saline solution. In the Heidenhain pouch animal the hypersecretion following alcohol was diminished after acidification of the duodenum (from a level of 91.3 mEq. per L. to 24 mEq. per L.). In the Pavlov pouch animals, this level dropped only from 137 mEq. to 106 mEq. per liter following acidification of the duodenum. The authors concluded that duodenal inhibition is mediated by a humoral mechanism as it is effective in animals with a denervated gastric pouch.

Instillation of acid into the jejunum has been shown by Sircus[66,67] to stimulate acid output from Heidenhain and Pavlov pouch dogs. He noted that this response could be abolished by the application of a 5% Procaine solution to the mucosa of the small bowel.

FAT IN DUODENUM. Sokolov[68] first noted that gastric secretion was inhibited by fat in the duodenum, and this was confirmed by Lim *et al.*[49]. Farrell and Ivy[25] demonstrated that the introduction of fat into the duodenum would inhibit the motility and the acid production of a totally denervated transplanted gastric pouch. This was confirmed by Gregory[29] who concluded that the inhibition of gastric motility and secretion was due to a humoral agent of duodenal origin.

For some time this humoral agent was assumed to be the chalone isolated from the mucosa of the duodenum by Kosaka *et al.*[45]. This material, enterogastrone, was extensively studied by Ivy's group[27] who felt that it was released by the proximal small bowel mucosa on contact with fat and demonstrated that it would inhibit gastric secretion in the dog that had been stimulated by feeding or by insulin. Later, Ivy *et al.*[41], utilized enterogastrone in the treatment of peptic ulcer patients and concluded that there was probably an anti-ulcer substance present in enterogastrone which might be effective in the treatment of duodenal ulcer. Howat and Schofield[35] noted that enterogastrone inhibited acid production in cats. An extensive analysis of enterogastrone is provided by Grossman[34] including its proof of existence, preparation and chemical properties, physiologic properties, mechanism of release and body actions. There have been many reports, however, which have demonstrated the ineffectiveness of enterogastrone as an inhibitor of gastric acid production. Benditt *et al.*[4] found that enterogastrone failed to inhibit gastric secretion in rats, and other reports[5,71] have demonstrated that it is of little use in treating peptic ulcer patients.

Sircus[67] demonstrated that fat placed into an isolated duodenal loop resulted

in no inhibition of gastric acid. When, however, this oil was mixed with pancreatic juice, incubated, and then placed into the duodenal loop, inhibition of gastric acid secretion resulted. Menguy[52,53,54] studied this problem and concluded that gastric inhibition caused by fat in the small bowel does not occur in the absence of bile salts and lipase. He stated that the inhibition of gastric output following bile duct ligation is due to the increase in the level of circulating bile constituents and concluded that the loss of the inhibition of absorbed fat is the cause of ulceration in pancreatic fistula patients. Sircus[67] felt that the inhibitory action of fat is a function of its osmolarity and does not begin until the fat had been digested with pancreatic lipase (presence of bile not required).

III. Augmentation of the Intestinal Phase by Porto-Systemic Anastomosis and by Liver Disease. CLINICAL EXPERIENCE. The increased incidence of peptic ulcer in association with cirrhosis has been noted by several authors[24,48,63], and Ostrow *et al.* in a review of this subject[57] reported the incidence of peptic ulcer in cirrhotic patients as varying between 1.8% and 25% in collected series. Fainer and Halsted[24] studied 200 patients with a clinical diagnosis of cirrhosis and found peptic ulceration in 18.4% of these. They reported 1278 consecutive necropsies in which Laennec's cirrhosis was found in 7.4%. Peptic ulceration was present in 17% of the cirrhotic patients and in only 10.6% of the non-cirrhotic patients, which difference was statistically significant. Clarke *et al.*[11] found no difference in the basal acid secretion or in the acid response to various stimuli between normal people, cirrhotic patients, and individuals following portacaval shunt. Ostrow *et al.*[57] reported a similar study in which they found that cirrhotic patients, whether clinically well or decompensated, all had a decreased secretion of gastric acid. Blood pepsinogen and uropepsin levels were diminished in post-necrotic, biliary, and alcoholic cirrhotic patients, indicating that the state of nutrition was probably not the cause of this. Cirrhotic patients with peptic ulcer were found to have higher levels of gastric acid secretion than patients with cirrhosis alone, but not as high as normal individuals. They felt that the incidence of peptic ulcer in cirrhosis was difficult to determine and that there were conflicting data on the frequency of co-existence. They suggested that slight relative elevation of acid in the face of diminished tissue resistance might be sufficient to cause ulceration.

Dubuque *et al.*[23] followed 60 patients with portacaval anastomosis for as long as 8 years and found that 15% of these developed an upper gastrointestinal ulcer. Clarke *et al.*[14] reviewed the evidence of increased peptic ulceration in patients following portacaval shunt and noted a personal experience of new peptic ulceration developing in 4 of 62 patients after shunting and exacerbation of a pre-existing ulcer in a fifth patient. The ulcer disease was severe in all, and it was felt that a possible causal relation existed between the shunting and the ulceration. Ostrow *et al.*[57] measured the output of gastric acid in a patient before and after splenorenal shunt. They found the basal hourly secretion of acid rose from 0.9 mEq. to 8.5 mEq. after shunting, and the output of acid following histamine went from 4.4 mEq. before shunting to 15.6 mEq. following operation.

EXPERIMENTAL STUDIES. Lebedinskaya[47] noted a great increase in the quantity and duration of gastric acid flow from Pavlov pouch dogs following portacaval shunt. She felt this was probably due to a diminution of the

detoxifying function of the liver and thought that this might explain the increased secretion of acid sometimes seen in cirrhosis. This study was confirmed by Gerez and Weiss[26], and they suggested that stimulants to gastric secretion were normally partially destroyed on passage through the liver.

Numerous recent reports confirm the experimental production of gastric hypersecretion following portacaval shunting[7,8,12,13,14,16,23,36,44,58,65] and following ligation of the portal vein[23,30]. Dubuque *et al.*[23] found that the acid output from Heidenhain pouch animals increased from 21 mEq. per day prior to operation to 63.9 mEq. per day after portacaval shunting. They noted that portal vein ligation caused a similar rise from a control level of 24.9 mEq. per day to 68.3 mEq. per day. In this same series, subsequent portavacal shunting was followed by an average daily Heidenhain pouch acid output of 67.8 mEq. per day. Clarke *et al.*[14] found an average increased acid output of 344% following portacaval transposition in Heidenhain pouch dogs. Kohatsu *et al.*[44] noted an increased Heidenhain pouch output of 537% following portacaval shunting, and a nearly identical increase in animals with a totally denervated gastric indicator pouch.

SITE OF ORIGIN OF STIMULANT. The increased gastric acid secretion of portacaval shunting was found to persist following antrectomy[14,16,30], isolation of the antrum[44], removal of the entire stomach except for a 1-cm. cuff at the cardia[58], vagotomy[44], splenectomy[65], pancreatectomy[65], and colectomy[65]. The persistence of the hypersecretion following antrectomy and vagotomy indicates that the site of the stimulus is probably the intestine. Clarke *et al.*[13] studied this possibility in Heidenhain pouch animals in which an anastomosis was accomplished between the superior mesenteric vein and the inferior vena cava. Following this procedure, blood from the intestine (from distal duodenum to mid-colon) was shunted around the liver, while blood from the pancreas, spleen, stomach and proximal duodenum still traversed the liver. In these animals there was a mean postoperative increase of acid output of 269%. When a subsequent portacaval transposition was performed, cephalad to the previous shunt, thereby redirecting the blood from the lower intestine through the liver, the acid output returned to control levels. They concluded that the agents responsible for hypersecretion following portacaval shunting arise from an area bounded by the distal duodenum and mid-colon. There is a recent report[7] that jejunectomy does not abolish the hypersecretion following portacaval shunting.

NATURE OF STIMULANT. Clarke *et al.*[14] noted that fasting caused a profound diminution in the gastric hypersecretion following portacaval shunt. This was confirmed by Silen and Eiseman[65] who noted a seven-fold decrease in the hypersecretion subsequent to portacaval shunting when the animals were fasted (although this value was still five times as great as the fasting output of the animal before transposition). Gregory[30] also noted that ligation of the portal vein increased the output of acid in the fasting animal. Pure protein meals were found to result in profound hypersecretion following portacaval shunting while meals of pure carbohydrate or fat produced less dramatic increases in secretion[65]. The ingestion of meat was found by Irvine and Code[37] to result in an increased concentration of urinary histamine, and they suggested that the histamine liberated into the portal vein following the ingestion of meat might be destroyed by the liver. Irvine *et al.*[38] noted that small subcutaneous doses

of histamine would increase the urinary output of histamine but would not stimulate acid output from a Heidenhain pouch. However, in these same animals following portacaval shunting, similar doses of histamine led to a significant increase in acid output as well as the appearance of histamine in the urine. They then administered aminoguanidine, an anti-histaminase, to Heidenhain pouch dogs and found that this increased the basal secretion of acid and further augmented the acid response to jejunal instillation of histamine. It has been demonstrated further[38,65] that histamine given via a systemic vein is a greater stimulant to gastric secretion than when given via the portal vein. Irvine *et al.*[38] and Silen and Eiseman[65] suggested that in the normal animal, histamine absorbed from the small bowel is deactivated by histaminase within the liver, and that in the animal following portacaval shunting, this absorbed histamine is allowed to enter the general circulation and stimulate gastric secretion.

Irvine *et al.*[39] suggested that the histamine in the portal vein blood following a meat meal is formed by the decarboxylation of l-histidine from meat by the flora of the gastrointestinal tract. Reducing this flora by succinylsulfathiazole administration resulted in a decrease in urinary histamine following a meat meal. On the other hand, Clarke *et al.*[13,14] have shown that the hypersecretion following portacaval shunting is not abolished by the administration of neomycin, which should similarly reduce the gastrointestinal flora[19].

RELATION TO VAGUS. Although Kohatsu *et al.*[44] showed that vagotomy would not diminish the hypersecretion following portacaval shunting, there is evidence that nervous mechanisms are somehow involved. Gregory[30] showed that animals with completely denervated gastric pouches and with portal vein ligation responded to teasing with food and to sham feeding with an increased output of gastric acid. The nature of this secretory stimulant released on vagal excitation is unknown. Cornish *et al.*[16] found that atropine would inhibit the hypersecretion following portacaval transposition.

INHIBITION OF HYPERSECRETION. Cornish *et al.*[16] demonstrated that the hypersecretion following portacaval transposition could be inhibited, before and after antrectomy, by acid in the duodenum, and intravenous administration of secretin, phenergan and atropine.

RELATION TO INTESTINAL PHASE. The persistence of the hypersecretion associated with portacaval shunting in animals following destruction of the cephalic and the antral phases strongly suggests that this increased acid production represents an augmentation of the intestinal phase of gastric secretion. Silen and Eiseman[65] demonstrated that this hypersecretion following shunting is chiefly stimulated by protein (similar to the intestinal phase), and Cornish *et al.*[16] showed that it is inhibited by the same mechanisms as the intestinal phase[56,66].

Conclusions. The identity of the intestinal phase stimulus is not fully known. Histamine has been shown to be involved in the intestinal phase of the normal animal following ingestion of meat. It has also been demonstrated that a hormone is released following distention of the small bowel. Whether endogenous histamine is this hormone is unknown. Certainly, however, decarboxylation of l-histidine from meat is not the only mechanism initiating the intestinal phase.

Following portacaval shunting the intestinal phase is augmented by failure of histamine inactivation. Fasting animals also show increased acid production following shunting, perhaps indicating that failure of inactivation of

endogenous histamine may also occur under these circumstances.

The importance of the intestinal phase of gastric secretion in normal individuals is difficult to assay. Dragstedt has estimated that it accounts for about 5% of the total acid output in normal dogs[20] and in peptic ulcer patients[21]. In a study of the various phases of gastric secretion, Sauvage *et al.*[61] noted that chronic histamine administration produced ulceration in 100% of the animals with the three stages of gastric secretion intact, while the single intestinal phase dogs developed ulceration in only 5% of the cases.

In contradistinction to this, however, lie the potentialities of the intestinal phase in patients with cirrhosis or portacaval shunting. If, as we believe, the intestinal phase is augmented in these situations, it may well largely contribute to the increased problem of peptic ulceration and gastrointestinal bleeding. For these reasons it would be of great importance to find means of inhibiting the intestinal phase.

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BOOK REVIEWS AND NOTICES

COLD INJURY, GROUND TYPE. By Col. Tom F. Whayne, MC, USA (Ret.) and Michael E. DeBakey, M.D. Pp. 570; 137 ills. Washington: Office of the Surgeon General, Department of the Army, 1958. Price, $6.25.

This is one of the best of a series of excellent volumes which record the official history of the Medical Department of the United States Army in World War II. As in previous wars, cold injury was an important cause of disability in World War II, with some 91,000 cases recorded. The enormous cumulative experience of these cases has been brought together, organized, and presented in an informative and instructive manner. There are chapters on every phase of cold injury, including its pathogenesis, clinical picture, diagnosis, treatment, prevention and control. The illustrations are of high quality, including those reproduced in color.

The authors are to be congratulated for an outstanding historical volume. It not only holds valuable lessons for the problem of cold injury during wartime, but also sets forth principles of management that may be followed in the handling of the less frequently encountered case in civilian practice.

C.Z.

THE NEW ILLUSTRATED MEDICAL ENCYCLOPEDIA FOR HOME USE. A PRACTICAL GUIDE TO HEALTH. Compiled and edited by Robert E. Rothenberg, M.D., Attending Surgeon, Jewish Hospital of Brooklyn. Pp. 1454; profusely illustrated, some in color. Four volumes boxed. New York: Abradale Press, Inc., 1959. Price, $50.00.

This four volume encyclopedia contains the answers to 7500 questions likely to be asked by patients and their relatives. It is a handsomely bound set, well indexed, and containing a host of excellent illustrations, including a set of superimposed layer plates of human anatomy. The answers to the questions are concise and any layman of average intelligence should have no difficulty in understanding them. Nineteen physicians, mostly from the Jewish Hospital of Brooklyn, and representing various specialties, have contributed, and little fault can be found with the answers.

The reviewer could not help wondering how many families will be willing to pay such a large price for an encyclopedia of medical knowledge. Will it not be true that those that do will include an unusually high percentage of persons overly concerned with health matters? And is it not possible that such a display of medical knowledge will tend to augment fears and foster new anxieties even though the authors have obviously done their utmost to avoid such an outcome? True, such persons have access to many popular articles on health in the lay press, but nowhere else are they likely to have their imagination stimulated in so many areas. It seems sad that Dr. Rothenberg's major reason for the encyclopedia's existence is the need to supplement the knowledge the too-busy physician gives to his patients. Is this not a condemnation of many physicians' practice? It seems to the reviewer that any physician who cannot find time to give each patient the carefully selected knowledge needed concerning his condition should either give up practice or alter his schedule and reduce his load of patients so as to correct this serious error. If this is not done the medical profession cannot hope to correct the very serious state of public relations existing today. T.D.

ANNUAL REVIEW OF MEDICINE, VOLUME 9, 1958. Edited by David A. Rytand and William P. Creger. Pp. 530. Palo Alto, California: Annual Reviews, Inc., 1958. Price, $7.00.

Twenty-eight different topics are reviewed in the present volume of this excellent series. All of the articles are timely and worthy of careful reading. Among the subjects discussed are the following: Bacterial Infectious Diseases, by E. M. Yow and R. L. Leacham; Viral Infectious Diseases, by F. M. Burnet and E. L. French; Diseases of the Gastrointestinal Tract, by H. M. Pollard and associates; Diseases of the Aorta, by S. H. Boyer, IV, and V. A. McKusick; Nutrition and Nutritional Deficiency Diseases, by R. W. Vilter and J. J. Will; Endocrinology, by S. P. Asper, Jr., and E. H. Wilson, Jr.; Allergy and Immunology: Autoimmunity in Disease, by F. J. Dixon; Diagnostic Radiology, by F. J. Hodges; and two chapters on laboratory aids to diagnosis and therapy, dealing respectively, with paper chromatography and electrophoresis (by E. L. Durrum), and enzymes (by H. A. Harper).

This volume is recommended to all internists and others interested in contemporary medicine. C.Z.

POLYSACCHARIDES IN BIOLOGY. Transactions of the Fourth Conference, May 21-23, 1958. Edited by GEORG F. SPRINGER, M.D., University of Pennsylvania. Pp. 326; 90 ills. New York: The Josiah Macy, Jr. Foundation, 1959. Price, $5.95.

THIS volume contains the proceedings of the Fourth of a series of Conferences on Polysaccharides in Biology held under the sponsorship of the Josiah Macy, Jr. Foundation. The conference followed the familiar pattern of its predecessors with basic presentations and discussions by the various participants. Topics considered include: Chondroitin Sulfates, by K. Meyer; Biology of Chondroitin Sulfates, by R. H. Follis, Jr.,; Heparin and Related Substances, by M. L. Wolfrom; The Mast Cell, by R. D. Higginbotham; and Biosynthesis of Sulfated Polysaccharides, by H. Boström.

Much valuable and stimulating information regarding these important biologic substances is contained in this volume. It is recommended to clinical investigators as well as to workers in the pertinent basic science areas. C.Z.

THORACIC SURGERY BEFORE THE 20TH CENTURY. BY LEW A. HOCHBERG, B.S., M.A., M.D., C.M., F.A.C.S., F.C.C.P. and F.A.C.C. Pp. 858; 155 ills. New York, Washington, Hollywood: Vantage Press, 1960. Price, $15.00.

THE absence hitherto of any adequate history of thoracic surgery makes this thorough and scholarly work—the result of the author's 20 years study in the field—all the more necessary and welcome. Among noteworthy features are the many quotations, even running to paragraphs, in the actual words of the author; the extensive Bibliography (some 2000 references included in 84 pages); the many illustrations—"a unique contribution to visual medico-historiography" in E. D. Churchill's words; important contributions unearthed by this erudite author that were apparently unknown to Billings ("The History and Literature of Surgery," 1895)—the extracts usually establishing their own right to inclusion. In general, the pleasant style contains a good number of informative items that promote relaxing reading, even if but a short time is available.

The unusual arrangement of having the first 5 chapters (from Prehistoric Times to the Nineteenth Century) cover the whole subject chronologically, then the next 8 chapters treating disorders grouped in parts of the body, necessitates some redundancy. This in turn may cause confusion or unnecessary labor in tracing some single concept through its history. The last chapter on Non-surgical Contributions (127 pages) includes 7 subdivisions ranging from Percussion to Peroral Endoscopy and X-rays. In the X-ray subdivision (the longest, 35 pages), the first half deals with physical items that have nothing to do with surgery and also are easily found in the literature. It could well be omitted.

Dr. Churchill's sprightly Foreword sets a pattern, though one would like to see at least one example of his disagreement with the author's interpretations and some of his reservations about "the conventional portrayal of the Rennaissance." Surprisingly, his name does not appear in either the Bibliography or Index of Proper Names.

Minor criticisms, such as the use of American rather than easily available English editions, occasional unexpected choices of words, for example, "the Erudite" for the 16th Century; the brief subject index (5 pages); a few typographical errors—all these are trivial, indeed, compared to the mass of interesting and, in general, accurate information presented to the reader. Dr. Hochberg has been thoroughly successful in his aim of presenting the contributions to the evolution of the practices in thoracic surgery before the 20th Century. We should all be grateful for his lucid characterizations of the great men of surgery and the presentation of their results. It is good, too, to know that "A Source Book of Thoracic Surgery in the 20th Century" is in preparation and is expected to be ready for publication sometime in 1963. E.K.

PRINCIPLES OF ORTHOPAEDIC SURGERY. BY PAUL C. COLONNA, M.D. Pp. 799; 500 ills., 10 in color. 2nd ed. Boston: Little, Brown and Co., 1960. Price, $22.00.

SEVERAL changes have been made in the second edition which have added to its value. It still remains an excellent textbook and as a reference book for the student in Orthopaedic Surgery. The author continues the regional outline which made the first edition unique from the standpoint of an orthopedic textbook. The additional material includes

many excellent illustrations which have brought the second edition up-to-date.

J.M.

CORONARY HEART DISEASE. By JOHN WILLIAM GOFMAN, M.D., PH.D., Professor of Medical Physics, University of California, Berkeley, California. Pp. 353; no ills. Springfield, Ill.: Charles C Thomas, 1959. Price, $8.00.

"TODAY an integrated framework of evidence does suggest that further delay in the application of a great fund of knowledge is no longer indicated" (in relation to the prevention of coronary heart disease). "Therapeutic nihilism is not the equivalent of a justifiable and well-founded conservatism in medicine." To these remarks of the author of this book, the reviewer cannot help but say a forceful, "Amen!"

Whether or not physicians agree on the utilization of the Atherogenic Index as the best means of deciding what persons should be placed on a prophylactic program and the exact nature of that program, the emphasis upon diet as the most important measure presently available, is becoming more and more generally recognized. That diets used should be considered "altered" rather than restricted is an excellent point, since it is possible to maintain excellent nutrition quite pleasantly and yet achieve entirely satisfactory results in shifting toward more normal lipid patterns in many individuals.

Dr. Gofman presents in a dispassionate and very readable manner his present views concerning his Atherogenic Index, together with a program based upon this and certain other factors such as hypertension, hypothyroidism, diabetes, obesity, and smoking. While dietotherapy is placed first in the therapeutic regimen, consideration is given to other means of influencing lipids such as thyroid substance, estrogens, heparin, nicotinic acid, beta-sitosterol, and others. It is a book which can be read with profit and enjoyment by all internists and cardiologists. T.D.

WORLD REVIEW OF NUTRITION AND DIETETICS. Edited by GEOFFREY H. BOURNE, Department of Anatomy, Emory University. Pp. 272; 56 ills. Philadelphia: J. B. Lippincott Co., 1960. Price, $12.00.

THIS is the first volume of a new series of nutritional reviews of international scope. The purpose of the World Review is to provide a forum for the extensive presentation of specific subjects in the field of nutrition by recognized investigators. An auspicious beginning is found in the leading article by Professor McCollum entitled "The History of Nutrition." This is a remarkable account of the development of animal experimentation and the roles of a multitude of workers whose efforts established the science of nutrition. From France, Guatemala, Japan, England, and United States, additional studies are published. Diverse topics are included such as the metabolism of protein, biosynthesis of vitamin C, kwashiorkor, vitamin B_{12}, anemia, neoplasia, isotopes in nutritional research, and nutritional requirements of embryos. The progress made in these subjects within recent years is critically and authoritatively discussed in the respective contributions. C.S.

PHYSIOLOGY OF PREMATURITY. Transactions of The Fourth Conference, Josiah Macy, Jr. Foundation. Edited by JONATHAN T. LANMAN, M.D., New York University. Pp. 187; 58 ills. Madison, New Jersey: Madison Printing Co., 1960. Price, $4.50.

THIS continuation of a series on the physiology of prematurity is a worthwhile summation of many studies on three major topics. Each is presented by a spokesman with liberal interchange among a group of panelists in the usual style of these familiar assemblies. The regulation of body temperature by the premature infant is discussed by S. Z. Levine and E. F. Adolph. J. A. Miller reviews the protective effects of hypothermia on asphyxia in the neonatal animal. The major account is the third which deals with chemical changes during development and the integration of renal function and growth. The leading discussant is E. M. Widdowson, from the renowned laboratory in Cambridge, England, where these last subjects have received studious scrutiny for some years. The abundant figures and tables, and the thoughtful annotation throughout, amplify the text admirably. A.B.

ACTUALITES NEUROPHYSIOLOGIQUES (Current Topics in Neurophysiology). Edited by A. M. MONNIER, Professor at the Sorbonne, Paris, and P. LAGET, Director of Conferences at the Faculty of Sciences, Paris. 1st Series. Pp. 276; 180 ills. Paris: Masson et Cie, 1959. Price, 42 NF.

THIS volume deals with a great variety of subjects such as the electric reactions in the olfactory system of the rabbit (Adrian), a

discussion of the relation of odor of a substance and its molecular structure (Guillot), the photoreceptors in the eye of limulus (Hartline), photo-activation of pigmented neurons in vertebrates (Arvanitaki-Chalazonitis), the role of Cl ions in the function of the Ranvier nodes (Stämpfli), the physicochemistry of the nerve membrane and probable role of monoglycerides (A.M. and A. Monnier), the reflex mechanisms regulating the sensitivity of intramuscular receptors (Granit), frequency limits in the central nervous system (Margaria), localization of reflex centres of respiration and vasodepression (Wyss), interaction between cerebral cortex and reticular formation (Bonvallet), discontinuous liberation of acetylcholin in the motor end plate (Katz), afferent innervation of muscles (Laporte), electromyographic studies in degenerated muscles (Humbert), cortical control of respiration (Coraboeuf), growth of the embryonic nervous system (May), integration of the secretion of the adrenal medulla in the activity of the sympathetic nervous system (Malmejac). These reviews written by an international team provide an excellent introduction to fascinating problems of neurophysiology. E.S.

ANATOMY: A REGIONAL STUDY OF HUMAN STRUCTURE. BY ERNEST GARDNER, M.D., DONALD J. GRAY, PH.D., AND RONAN O'RAHILLY, M.SC., M.D. Pp. 1024; 657 ills. Philadelphia: W. B. Saunders Co., 1960. Price, $15.00.

To meet the needs of the undergraduate medical student in the present shortened course in anatomy, this new didactic textbook departs far more than all other recent short anatomy texts in an attempt to correlate and integrate the student cadaver dissection with functional anatomy, as observable in the living body and as met with and applied in the practice of medicine. After a preliminary explanation of the fundamental principles of systemic anatomy, the authors in their text follow a regional approach.

Outstanding merits of this book are: (1) brief history of anatomy with a listing of standard anatomy books, atlases, and periodicals; (2) clear, concise description of anatomic structures, variational patterns are seldom mentioned but references to articles dealing with them are many and pertinent; (3) brief, helpful resumes of the comparative anatomy and development and, frequently, of the histology of organs; (4) instruction on surface anatomy and palpable structures with changes thereof in movements and as used in physical diagnosis; (5) an introduction to radiological anatomy, its technique and manifold illustrations of its application to the skeletal and soft parts of the body, most of the 65 plates being devoted to radiograms; (6) brief account of the function of organs, nerves, blood vessels and lymphatics as ascertained in normal and experimental physiology and in clinical medicine with frequent references to abnormal conditions and congenital defects; (7) concise, clear description of the gross structure of the brain, cranial nerves, ventricles, meninges, and blood supply, the internal structures of the brain being left to texts of neuroanatomy; (8) a very comprehensive bibliography, references to pertinent contributions, written in the English language, being placed as footnotes practically on every topic discussed; (9) a highly informative and much needed glossary on eponymous terms (5 pages), as the text avoids proper names and follows strictly the *nomina anatomica* of Paris; (10) an excellent index; (11) ample number of figures in black and white, albeit that the vast majority of them are too black and not artistically nor naturally drawn, especially as regards striated musculature (external intercostals, soleus, shoulder muscles).

In view of the vast amount of clinical anatomy contained in this book, one wonders whether it will lighten the average freshman's task of learning fundamental, elementary anatomy, of which he knows very little when entering a medical school. All too many items described from a functional and clinical point of view, the student will have sufficient time to learn in his subsequent medical courses, in physiology, physical diagnosis, neurology, radiology, orthopedic surgery, and others.

In textual content and richness of bibliographic references, the book affords the brighter freshman student ample opportunity for advanced study far above that at present given, or possible, in anatomy courses at most medical schools. From an instructive point of view, the book could advantageously be owned by every medical student, as highly useful in his medical training, and by every physician, as a short review of what we should know about body structure and function. N.M.

PRATIQUE OBSTETRICALE. VOL. I AND II. BY M. LACOMME, Professeur de clinique a la Faculte de Medecine de Paris. Membre de

de L'Academie Nationale de Medecine. Pp. 1719; 308 ills. Paris: Masson et Cie, 1960.

THIS two volume "Pratique Obstetricale" was prepared for use as a student textbook as well as for a reference for practicing physicians. Unlike many other similar texts this one actually can be used to advantage by both groups. The material is presented in an interesting informal style much more like a lecture on clinical ward rounds than a textbook. The material, which is presented in detail, includes the historical background, pertinent anatomic and physiologic material, methods of diagnosis and directions for the management of each subject discussed. Directions are given in great detail and are specific, several diagnostic and treatment procedures are described for each special circumstance, but the author rarely fails to evaluate each and to indicate which he has found most effective and which he prefers. This attention to detailed analysis rather than simply presenting the material is the reason why the book should be attractive and useful at all levels of experience.

The first volume is devoted to normal pregnancy and delivery and to certain complications such as hemorrhage, abnormal presentations, dystocia and the puerperium. Much attention is given to the details of obstetric physiology in appropriate places; for instance 28 pages are devoted to the myometrial physiology. The psycho-physical management of labor is considered in great detail. The author concludes that one should expect little alteration in the mechanism and duration of labor in trained patients; he seeks normal rather than painless labor. Contracted pelvis is discussed exhaustively and there are numerous well reproduced roentgenograms to illustrate the various types.

The second volume is devoted to the major complications of pregnancy such as abortion, ectopic pregnancy, toxemia, medical and surgical complications, and others. In addition there is an excellent section on the care of the newborn infant and another on fetal and maternal mortality.

The methods used and endorsed by the author are for the most part like those in general use in this country. In many instances, however, nomenclature is unfamiliar. The illustrations are rather sparse and for medical students particularly the text is inadequately illustrated. There are several excellent colored reproductions of gross lesions and photomicrographs. The line drawings of operative procedures, while adequate, sometimes are a little crude by standards in this country. J.W.

GLAUCOMA. Transactions of the Fourth Conference, March 8, 9 and 10, 1959, Josiah Macy, Jr. Foundation. Edited by FRANK W. NEWELL, M.D., Department of Surgery, University of Chicago. Pp. 257; 108 ills. New York: Josiah Macy, Jr. Foundation 1960. Price, $8.00.

THE transactions of this Fourth Conference maintain the high standards of the others. This group of timely topics, on some of the basic problems in glaucoma, should be read by all persons interested in understanding the scientific work going on in ophthalmology and other related fields.

These areas of discussion are covered in such a fashion that many related subjects are welded into the considerations. We can follow, step by step, the high points of interest that these various authorities considered imperative for an understanding and attempted solution of the problem. Directions of further investigation are suggested and costly time-consuming errors are noted. This book is a must for anyone doing research or seriously following developments in glaucoma or related fields. L.H.

THE POPULATION EXPLOSION: ITS MEANING FOR HEALTH AGENCIES. Pp. 128; illustrated. Harrisburg, Pa.: Pennsylvania Health Council, 1959. Price, $1.00.

THIS booklet incorporates the proceedings of the Ninth Annual Meeting of the Pennsylvania Health Council, at Harrisburg, on March 18, 1959. Authorities from several fields review the problems of expanding population in panel discussions on: A. Organization of Health Agencies, B. Effective Use of Manpower, C. Health Facility Needs and Uses. Problems and challenges cited in the text are supplemented by demographic charts.

In the past, famine, pestilence and war kept world population in control, as did a tragic infant mortality. Preventive medicine, improved nutrition and living conditions, while increasing longevity, have posed problems of population increase—particularly in China and India, which will strain existing social and technical fabrics. Demographers forecast that the world population of 2.5 billion today may expand to 6 or 7 billion by the year 2000. Productive agricultural and industrial methods compensate somewhat, but diminishing natural resources are an increasing hazard. Diseases, by virtue of their altered patterns, cannot serve now to limit populations as they did in the past. The role of health agencies in a period of population

pressures and global tensions is reviewed in this interesting publication. F.R.

RADIATION BIOLOGY. Proceedings of the Second Australasian Conference on Radiation Biology, held at the University of Melbourne, December 15-18, 1958. Edited by J. H. MARTIN. Pp. 304; 82 ills. New York: Academic Press, Inc., 1959; London: Butterworths Scientific Publications, 1959. Price, $11.00.

THIS is a collection of papers presented at an Australian conference on radiation biology in December, 1958. A wide variety of subjects is covered, ranging from a superb discussion of macroscopic and microscopic aspects of radiation dose by Gray to actions of radiations on simple organic compounds, and on to a discussion of human implications. Outstanding is a chapter on leukemia induced by radiation, by Loutit, which should be read by every scientist who wishes to consider himself informed on the subject of radiation-induced leukemia. It should be mandatory reading for physicians. In this chapter, Loutit explores the simple relationships which have been recently proposed as operative causatively in the radiation induction of leukemia, and demonstrates that the linear relationship, the absence of a threshold, and the somatic mutation concept of such leukemogenesis are all insufficient, and naive over-simplifications of the complex factors involved. That such over-simplifications in the case of leukemia are invalid is apparent on reading Loutit's chapter; this reviewer feels that the same remarks may also be extended to the simplified hypothesis of carcinogenesis in general, especially as regards the somatic mutation theory of carcinogenesis in general, and of a simple virol etiology of cancer in general.

Also admirably discussed in other chapters are current progress in the status of bone marrow transplantation and homograft survival, secondary radiation disease following hederografting, many chapters on alteration of radiosensitivity of both by means by altering oxygen tension, and by administerating radiation protecting or sensitizing agents.

Contributing further to the great value of the book are chapters on the life span of mutagens produced in cells by irradiation, a chapter on the sensitivity of germ cell stages to irradiation, and a final chapter on radiobiologic mechanisms at the cellular level. These key chapters make this small book an essential member of every library dealing with the effects of radiation. R.R.

LE CORTEX CÉRÉBRAL. By J. DEAJURIAGUERRA, Professor of Psychiatry, Faculty of Medicine, Geneve, and H. HÉCAEN, Physician to the Psychiatric Hospital. 2nd ed. Pp. 458; 38 ills. Paris: Masson et Cie, 1960. Price, 46 New francs (approximately $5.00).

THIS soft cover volume is written in French. This second edition closely follows the outline of the first; however, it has been completely revised to include the latest knowledge of cerebral cortical function. The book is divided into two parts. The first deals with anatomical clinical syndromes as follows: frontal syndrome, rolandic, the syndrome of the corpus callosum, parietal syndrome, temporal and occipital syndromes.

The second part describes neuro-psychopathologic problems, such as: Aphasia, apraxia, astereognosis, auditory, and visual agnosia, hallucinations and focal cortical lesions.

This volume should be of interest to neurologists, neurophysiologists, neurosurgeons, and psychologists who are concerned with the many complex problems of cerebral function and localization. M.S.

A SYMPOSIUM ON IMMUNIZATION IN CHILDHOOD. Edited by D. A. CANNON, W. C. COCKBURN, D. G. EVANS, AND H. J. PARISH. Pp. 139; 5 ills. Edinburgh & London: E. & S. Livingstone Ltd., 1960 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $4.25.

THE proceedings of a 3-day symposium dedicated to the subject of immunization in childhood are briefly recorded herein. Numerous participants, predominantly from the British Isles and representing expert opinion from various related fields, have contributed. The complications of immunization and technical precautions are considered in the early sections of the volume. The matter of mixed versus single antigens is discussed. An extended discussion closes the sessions, with recommendations for a schedule of immunization beginning during infancy. The commencement of the program in early life and its completion in a minimum number of visits is stressed. BCG appears as a routine recommendation at 10 to 15 years age, unless the risk of exposure justifies earlier vaccination. The subject, while interesting, is not sufficiently detailed for the student of the subject. As a handbook of practical information for the physician, it contains little more detail on the subject than is to be found in a stand-

ard current textbook of pediatrics. However the thoughtful management of the problem may lead to further symposia of greater value, of which this may be regarded as introductory.

A.B.

ESSENTIALS OF ORTHOPAEDICS. By PHILIP WILES, M.S. (LOND.), F.R.C.S., F.A.C.S., Senior Orthopedic Surgeon to the Middlesex Hospital. 3rd ed. Pp. 576; 417 ills. Boston: Little, Brown & Company, 1959. Price, $13.00.

DR. WILES original text on Essentials of Orthopedics was printed in 1949. The present, third, edition, was printed in 1959. The foregoing indicates that a demand must exist for the text and after reviewing the current edition it is apparent that the demand will continue for a long time. The text is confined to pure orthopedics. Fractures, their treatment and complications, are omitted; and rightly so. The subjects covered are varied and practical. The author has a style that bespeaks conciseness and lucidity. The illustrations are well done and abundant.

The text can be readily recommended for medical students, interns, residents and orthopedists. The reference is of valuable aid for any desiring further information relative to any of the topics discussed.

A.S.

CLINIQUES RADIOLOGIQUES. By PROFESSEUR J. ROUSSEL AVEC LA COLLABORATION DE P. SCHOUMACHER, M. PERNOT, ET R. POIRÉ, Chaire d'Electroradiologie Clinique de la Faculte de Medecine de Nancy. Pp. 102; 59 ills. Paris: Masson et Cie, 1959. Price, 3200 fr.

THIS book emphasizes the important place (and also the limitation) of the radiographic examination in problems involving the base of the skull. Details possible in evaluating the petrous portion of the temporal bone, with particular reference to fractures here, are well demonstrated.

The first chapter deals with physical factors (size and density of the object, dosage employed).

The second chapter is concerned with technique and interpretation of radiographs of the base of the skull and of the anterior, middle, and posterior fossae. The illustrations and drawings are excellent.

The third chapter discusses the modern classification of fractures of the petrous bone.

The final chapter is a superb collection of cases illustrating small fractures through the petrous bone. Drawings accompany the radiographs. Errors in interpretation are discussed. A lengthy bibliography accompanies the work.

This is a job well done and is an authoritative and valuable reference, particularly for radiologists, otologists and neurosurgeons.

H.W.

DIE MÄNNLICHE KEIMDRÜSE. STRUKTUR. FUNKTION. KLINIK. GRUNDZÜGE DER ANDROLOGIE. By E. TONUTTI, O. WELLER, E. SCHUCHARDT AND E. HEINKE. Pp. 187; 38 ills. and an atlas of 31 plates. Stuttgart: George Thieme Verlag, 1960. Price, 79 DM.

THIS is a comprehensive monograph (668 references). An introductory section deals with the embryonal development of the gonad. There follows a discussion of five "levels of manifestations of sex:" genetic, germinal, gonadal, "gonophoric" (genital tract), and somatic. The next sections deal with the anatomy of the testis, the pituitary-testicular "system" (including chemistry and assay of gonadotropin), the andorgens (chemistry and metabolism), the actions of androgens, the ejaculate (morphology, chemistry, technique of examination), puberty. The following sections deal with the clinical problems of hypogonadism, infertility, delayed puberty, precocious puberty and pseudopuberty, cryptorchidism, and testicular tumors. The last section covers diagnostic techniques (gonadotropins, 17 ketosteroids, bone age determination, anthropometric (somatometric) measurements, testicular biopsy, sex-chromatin determination. The presentation is clear and authoritative. The most distinctive feature of this book is the atlas of 31 plates containing superb microphotographs. A very valuable book indeed.

K.P.

EDEMA. MECHANISMS AND MANAGEMENT. A Hahnemann Symposium on Salt and Water Retention. Edited by JOHN H. MOYER, M.D., and MORTON FUCHS, M.D., Hahnemann Medical College and Hospital. Pp. 833; illustrated. Philadelphia: W. B. Saunders Company, 1960. Price, $15.00.

A SYMPOSIUM on the mechanisms and therapy of edema was held recently at the Hahnemann Medical College and Hospital. The material presented and the discussions engendered are made universally available in this book. There are 123 contributors providing information from basic through clinical levels. Part I is concerned with fluid and electrolyte balance, part II with the pharmacology and therapeutic use of diuretics, part

III with iatrogenic edema, part IV with hypertension, part V with toxemia of pregnancy and premenstrual tension, part VI with edema of renal origin, part VII with edema associated with liver disease and part VIII with congestive heart failure. Consideration of such diverse problems by men actively engaged in their solution has afforded us the opportunity to keep abreast of current thinking. The editors are to be commended for bringing such information to us, conveniently and especially so soon following the symposium. J.Z.

CHROMATOGRAPHIE: EN CHIMIE ORGANIQUE ET BIOLOGIQUE. VOL I. GÉNÉRALITÉS, APPLICATIONS EN CHIMIE ORGANIQUE. VOL. II. APPLICATIONS EN CHIMIE BIOLOGIQUE. Edited by E. LEDERER, Professor of the Faculty of Science of Paris. Pp. 672 and 876; 164 and 98 ills., respectively. Paris: Masson et Cie, 1959 and 1960. Price, 10,000 and 14,000 fr. (about $22.00 and $33.00).

THESE two volumes comprise a most important addition to the reference library of those working in organic and biological chemistry. The techniques of chromatography have solved easily so many otherwise difficult separation problems and made possible the attack on other problems thought out of reach, that it will be a part of the thinking and part of almost every piece of laboratory research from now on.

It was the goal of the editor to give sufficient background and detail so that, for most workers, reference to the original literature will not be necessary. The various sections are written by experts working in the fields using chromatographic separation techniques.

Volume I deals with general principles, and theories of adsorption, ion exchange, and gas chromatography, on columns and on paper strips, and covers the techniques of radio-isotopic chromatographic applications. In addition, Volume I describes the specific application of these principles by clearly outlined techniques to the separation of, for example, hydrocarbons, alcohols, nitrogenous compounds, alkaloids, halogen compounds, and stereo-isomers, to mention a few. The bibliography for Volume I contains some 3200 references to the original literature.

Volume II extends the consideration of specific techniques to substances of more biological interest such as sugars, phosphoric esters, sterols, amino-acids, proteins, vitamins, hormones, antibiotics, and others. A bibliography comprises about 3800 references.

This is a clearly written, well annotated, extremely valuable reference text for this field, which is notably diffuse in the scientific literature. The binding and printing are of the usually excellent Masson et Cie quality. J.B.

DÉGÉNÉRESCENCE HÉPATO-LENTICULAIRE. By G. BOUDIN, Associate Professor of the Medical Faculty of Paris and B. PEPIN, former Chief of the Neurological Clinic of the Medical Faculty. Pp. 250; 46 ills. and 1 color plate. Paris: Masson et Cie, 1959. Price, 3.500 fr.

THE authors have accumulated significant information on Wilson's disease (hepatolenticular degeneration). The book, after a brief historical review, offers the reader the various considerations such as etiology, race, sex, age, heredity, clinical and neurological manifestations. This is followed by a discussion of liver function, pigmentary and other metabolic disturbances. The pathological findings in the central nervous system, the liver, the eye, the spleen and other organs are amply illustrated. A differential diagnosis is followed by a discussion of the biochemical disturbances associated with this disease, ending with a critical examination of the significance of these abnormal findings. The book also includes a chapter on therapy. Throughout the book, the authors frequently refer to world-wide literature on the subject. This is indexed as 714 references. In an appendix, the authors present in detail, 9 cases of their own. The book is well written in a concise and factual style, with clear-cut subdivisions for each aspect of the disease so that the reader may readily refer to the section of immediate interest to him. This compensates amply for the lack of an index. The book is worthy reading material for any one in the medical field. E.L.

CARCINOMA OF THE THYROID GLAND. By STUART LINDSAY, M.D., Professor of Pathology, University of California School of Medicine. Pp. 168; 18 photomicrographs. Springfield, Ill.: Charles C Thomas, 1960. Price, $8.50.

THIS is a comprehensive study of 293 cases of thyroid carcinoma, tracing the lesion from its incipiency to its conclusion and demonstrating its varying facets and growth patterns. The literary style of the author makes for easy reading and the tables are well illustrative of the thoroughness of the author's endeavors. A sense of humor can also be de-

tected on page 27 where the author quotes Searls as stating that "the thyroid nodule in a female patient who is beautiful is likely to be carcinoma, although it has been pointed out that this sign cannot be used by older physicians since to them all women may appear beautiful." The author emphasizes that a statistical relationship exists between carcinoma and Hashimoto disease and that the carcinoma usually associated with this disease is of the papillary type. Another important point is the subgrouping of follicular carcinoma into three histopathological types namely the follicular variant of papillary carcinoma, the localized follicular carcinoma and the invasive follicular carcinoma. In his concluding chapter the author gives his reasons for radical surgery, although indicating that the evaluation of any form of therapy would require an analysis of large groups of patients and suggesting that such study be undertaken by the American Goiter Association.

A.P.

THE INTESTINAL TRACT. By RICHARD PAUL SPENCER, M.D., Whitney Research Fellow in Chemistry, Harvard Medical School. Pp. 411. Springfield, Ill.: Charles C Thomas, 1960. Price, $12.75.

THE author attempts to provide an understanding of the intestine by emphasizing the basic concepts of structure, function and pathology. The book is divided into 3 sections dealing with methods of study, intestinal functions and its modifiers, and disorders of intestinal function. The approach to organization of material is different, simple and written in excellent style. Chemical considerations of absorption, enzymology, metabolism and electrolyte physiology are obviously the authors major interests and consequently are the best sections in the book.

Major criticisms of the book fall into 4 categories; omissions, brevity to the point of failing to make data clear, acceptance of "newness for newness's sake" without critical analysis and inclusion of skimpy clinical descriptions of a few diseases which add nothing vital to a consideration of basic concepts of disease.

Among major topics omitted from consideration are gastric secretion and electron microscopy. Although the author states that ideally the prime focus of function is the cell, he fails to enumerate the startling advances made in our understanding of gastrointestinal diseases by the electron microscopists. Pharmacological discussion is limited, for practical purposes, to the enumeration of cathartics. A chapter on "some effects of diet and psyche" is so superficial that it is worthless. The same may be said for the authors treatment of the few diseases that he discusses.

In spite of the criticisms listed above, this book has much of value and is a needed text. When it is rewritten, the author should stick to his goal and emphasize basic concepts of intestinal disease, omitting descriptions of disease states. Pancreatic, gastric and biliary secretion should be included and chapters, such as that on methodology, should be more complete. The reader will enjoy this text but will probably conclude, as did this reviewer, that the author should have had the courage to pursue his original aim. S.L.

INHERITANCE OF GLIOMA. By H. J. VAN DER WIEL, Consulting Neurologist, Municipal Hospital, Gouda, The Netherlands. Pp. 275. Amsterdam: Elsevier Publishing Company, 1960; Princeton: D. Van Nostrand Co., Inc., 1960. Price, $12.50.

THIS is a remarkable and comprehensive study on the significance of genetic factors in the development of cerebral tumors. The author examined the relatives of 100 patients chosen at random with glioma of the brain and concluded that status dysraphicus was an important predisposing factor in the production of glioma. Status dysraphicus was first described by Bremer as a disposition for syringomyelia. In addition to status dysraphicus the author noted that in the tumor group the frequency of cafe-au-lait spots was much higher than in the control group and that there was a positive correlation between status dysraphicus and cafe-au-lait spots. He concludes that the pigment anomaly is caused by the presence of a specific gene, which is also significant for the origin of gliomas. Van Der Wiel believes that gliomas are manifestations of an endogenous blastomatosis. This is an extremely interesting book for the geneticist and for the oncologist. A.P.

THE ETIOLOGY OF SCHIZOPHRENIA. Edited by DON D. JACKSON, M.D., Director of the Mental Research Institute of the Palo Alto Medical Research Foundation. Pp. 456; 3 ills. New York: Basic Books, Inc., 1960. Price, $7.50.

In this volume the reader finds varying points of view along the bio-social continuum of etiology. Seventeen contributors, experts in the field, present their views regarding the genesis of schizophrenia. All major points of

view, the genetic, biochemical, physiological, psychological and family dynamics are included.

Many of the authors are well known authorities. The book is unusually well organized. The subject is reviewed extensively and intensively. It highlights the difficulties encountered in the field. This contribution is required reading for all interested in the subject of schizophrenia. M.B.

PSYCHOANALYSIS AND THE FAMILY NEUROSIS. By MARTIN GROTJAHN, M.D., Associate Professor of Psychiatry at the University of Southern California. Pp. 320. New York: W. W. Norton and Co., Inc., 1960. Price, $5.95.

THE author considers his book as describing a new direction in analytic technique. He states that the psychoanalytic treatment of a married couple or a family must aim at the understanding and therapy of the complementary neurosis; that is, the way the patient's unconscious communicates with that of his marriage partner, or with those of the other members of his family.

Grotjahn believes that the dynamics of family interaction show important resemblances to the essentials of the therapeutic analytic process and that the family may be considered as an extension of the individual's personality.

In the opinion of this reviewer, Grotjahn's book leans toward environmentalism in psychopathology and away from psychoanalysis. His techniques may be indicated in the treatment of children and of psychotic patients, but are appropriate to the psychoanalytic treatment of neurosis. This book may be a contribution to psychotherapy but it is unfortunate that Grotjahn summons psychoanalysis as a witness for it. M.B.

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pH AND BLOOD GAS MEASUREMENT. Edited by RONALD F. WOOLMER, V.R.D., B.A., B.M., F F.A.R.C.S., Professor of Anesthetics in the Royal College of Surgeons of England. Pp. 210; 52 ills. Boston: Little Brown and Company, 1959. Price, $8.50.

THIS book is the report of a meeting of individuals interested in the field of hydrogen ion (pH) regulation of the blood and the problems of the measurements associated therewith. It included biochemists, physicists, pediatricians, surgeons, anesthetists, physicians, clinical pathologists and urologists; for all of whom, interest in the subject transcended professional dividing lines.

No existent textbook joins the lines of thought necessary to a discussion of this type; nor is the information easily available in the periodical literature. The report is presented, as are previous Ciba symposia, in the form of a series of formal papers, followed by what is apparently an (almost) verbatim record of the informal discussion which followed.

The result is extremely informative and challenging to physicians and surgeons in all fields and clinical chemists as well. It suffers only from the inevitable defects of a transcribed verbal exchange (which overall, adds rather than detracts from the value of the report).

The volume includes discussions of the pH measurements by glass electrode, standardization problems, estimation of pCO_2 (by various procedures), new blood O_2 and CO_2 electrodes, and a discussion of equipment features. Also included is a valuable discussion of the clinical significance of the results obtained by the newer procedures in medical, surgical and anesthetic cases.

The Ciba foundation is to be commended for its continued support of this type of symposium. J.B.

KRANKHEITEN DER TIEFEN VENEN DER UNTEREN GLIEDMASSEN. By DR. MED. IVO PREROVSKY, DR. MED. JIRI LINHART UND DR. MED. RUDOLF REJDAR, Institut für Kreislaufforschung in Praha/CSR. Pp. 127; 54 ills. Jena: Gustav Fischer Verlag, 1960. Price, 15,80 DM.

THIS book contains a detailed description of studies of the subcutaneous and deep veins of the lower extremities and their anastomoses by the Brodie-Trendelenburg test, Perthes test, phlebography and a new method to measure changes in the blood pressure in the veins under various experimental conditions. It was possible by these methods to distinguish between diseases of the cutaneous and deep veins, and between obliteration of the vessels and valvular insufficiency. Both phlebography and pressure determinations were carried out in 81 persons. For the diagnosis of obliteration, phlebography was found to be more sensitive, while for chronic valvular insufficiency of the deep veins pressure tests gave better results. A clinical study of 301 ambulant patients permitted their classification in 173 cases of primary varices, 46 cases of thrombosis, 39 cases of phlebitis and

43 cases of edema. Measurement of venous pressure in these patients revealed disturbances in the deep veins most often in cases of thrombosis, but also in 25% of cases of varices. In the last chapter prevention and therapy are discussed. The text is well illustrated. The bibliography contains 199 references. The book is highly recommended to all students of the veins of the lower extremities. W.E.

ELECTROCARDIOGRAPHIC TECHNIQUES. A MANUAL FOR PHYSICIANS, NURSES AND TECHNICIANS. By KURT SCHNITZER, M.D. 2nd ed. Pp. 109; 62 ills. New York and London: Grune & Stratton, Inc., 1960. Price, $4.75.

ELECTROCARDIOGRAPHY is a widely used method. A prerequisite for interpretation is correctness of the underlying technical procedures. This book offers a most welcome help. Starting out with a detailed description of the instrument and its accessories, of the room, and of the preparation of the patient, the detailed procedure of the recording is outlined, followed by a discussion of the distortions of the graph and the precautions to eliminate them. Finishing, mounting, and filing of the record are described. Special procedures are given in detail, such as exercise test, fetal electrocardiography, examination of infants, esophageal and endocardial studies and special devices are mentioned, including phono-, ballisto-, and vectorcardiography. The recommendations of the American Heart Association Committee are reprinted verbatim. There are references from the literature. This book, easy to read, and well illustrated, is highly recommended. H.R.

TASCHENBUCH KLINISCHER FUNKTIONSPRÜFUNGEN. Edited by PROF. DR. DR. H.C. MED. A. GITTER, Arztlicher Direktor des Bergarbeiterkrankenhauses, Stollberg/Erzgeb. and PROF. DR. LUDWIG HEILMEYER, Direktor, Medizinischen Universitats-klinik, Freiburg/Br. Vol. 23. Pp. 521; 112 ills. Jena: Gustav Fischer Verlag, 1960. Price, DM 18.

THIS helpful book contains concise descriptions of some 300 function tests of heart, blood vessels, lungs, gastrointestinal tract, liver, kidneys, endocrine glands, blood and spinal fluid which are used at the Miners Hospital at Stollberg and the University Hospital at Freiburg. Each section is preceded by a brief summary of the pathophysiology and clinical symptomatology of the disturbances concerned and of the patho-physiological principles involved. The sources of errors are also presented. The book was published first in 1955. It is now in its 6th edition. It is highly practical and up-to-date. It contains such modern techniques as lipidelectrophoresis, quantitative determination of urobilin and methods for the measurement of enzyme activity in myocardial infarction. This excellent book is highly recommended to clinicians and pathologists who read German. W.E.

KLINISCHES LEHRBRUCH DER PHYSIKALISCHEN THERAPIE. Edited by PROF. DR. J. GROBER, Director of the Institute of Physical Therapy of the University of Jena, ret. 3rd revised edition. Pp. 442; 276 ills. Jena: VEB Gustav Fischer Verlag, 1960. Price, DM 37.75.

THE new edition of Physical Therapy was brought up-to-date and greatly improved by well selected drawings and illustrations. Guided by the master hand of Grober, eight contributors present in a well rounded, readable, and lucid way a wealth of theoretical and practical information. The inclusion of radium and Roentgen-ray therapies enhances the value of this book even though they are generally not regarded as the domain of physical medicine. European and Soviet physicians rely heavily on spa, resort and thalasso therapy as a popular extension of a modified hospital routine. This form of rehabilitation, accommodating millions of chronically ill or otherwise handicapped persons, is discussed in detail by two of the foremost experts in this field. It is regrettable that the language barrier limits the use of this excellent text. I.K.

METAL-BINDING IN MEDICINE. Edited by MARVIN J. SEVEN, M.D., AND L. AUDREY JOHNSON. Pp. 400; illustrated. Philadelphia: J. B. Lippincott Co., 1960. Price, $13.75.

RAPID and widespread developments have occurred in the trace metal field in recent years. These have included a number of interesting basic research findings and early applications to certain areas of clinical investigative therapy. In order to bring together as much of the contemporary information as possible regarding the uses of metal-binding agents in medicine a symposium was held at the Hahnemann Medical College, Philadelphia, in May, 1959. This book is a collection of the formal papers and discussions presented at that meeting. It is recommended as a basic reference volume for information concerning this important new area in medicine. C.Z.

Bedside Diagnosis. By CHARLES SEWARD, M.D., F.R.C.P. (EDIN.), Physician, Royal Devon and Exeter Hospital (Great Britain). 5th ed. Pp. 479; 15 ills. Baltimore: The Williams & Wilkins Co., 1960. Price, $6.00.

THIS is the fifth edition of this British handbook. The differential diagnosis of common symptoms and signs is outlined. There are many inaccuracies, some inherent in this shortcut method. This book is not recommended for medical students or practitioners. W.S.

Molecules and Mental Health. Edited by FREDERIC A. GIBBS, M.D., Professor of Neurology, University of Illinois College of Medicine. Pp. 189; 52 ills. Philadelphia: J. B. Lippincott Co., 1959. Price, $4.75.

THIS volume consists of papers presented at two conferences which were devoted to recent developments in the field of psychopharmacology. The first dealt with "Amines in Relation to Brain Function and Behavior" and included discussions of ceruloplasmin, taraxein, ergot hallucinogens, tryptophan metabolism, epinephrine, norepinephrine, and acetylcholine. The second conference was concerned primarily with Hypsarythmia and its treatment with ACTH and cortisone.

Investigators in psychiatry, neurology, pharmacology, neurophysiology and related disciplines will find much of interest in these articles.

C.Z.

Medical Research and the Death Penalty. By JACK KEVORKIAN, M.D. Pp. 75; 1 ill. New York: Vantage Press, Inc., 1960. Price, $2.50.

IN this small volume the author raises a big question: Should a condemned criminal be permitted to choose anesthesia and medical experimentation upon his body as an alternative to present-day methods of execution? The writer's view that this should be allowed is presented in an imaginary dialogue between a protagonist and an antagonist to the proposal.

The suggestion strikes the reviewer as a controversial addition to the already highly complex socio-legal aspects of the death sentence as well as to the philosophic and legal considerations of experimentation on human beings. C.Z.

An Introduction to Psychoanalytic Research. By KENNETH MARK COLBY, Research Chairman of the San Francisco Psychoanalytic Institute. Pp. 117. New York: Basic Books, Inc., 1960. Price, $3.00.

IN this brief and interestingly written book, Dr. Colby points directions whereby scientific observation, experimentation and verification may be adapted to the established psychoanalytic framework.

The author's essential thesis states that to see a problem, to feel it is worth solving, and to search, guided by hypotheses, for the hidden explanatory pattern constitutes the essence of discovery. The psychoanalyst must derive new hypotheses, press a search for the relevant facts of crucial regularities, measure those facts, and formulate their explanatory principles.

Psychoanalytic search intends to contribute to a science of persons. This is best accomplished within the psychoanalytic situation where the effect of person upon person is intensified.

M.B.

Letters of Sigmund Freud. Selected and edited by ERNST L. FREUD, Son of Sigmund Freud. Pp. 470. New York: Basic Books, Inc., 1960. Price, $7.50.

PERSONAL letters written by Sigmund Freud between the years 1873 and 1939 comprise this collection. The arrangement of the material is purely chronological. More than one-third of the correspondence consists of love letters written to Martha Bernays. There are other letters to notable figures such as Albert Einstein, Thomas Mann, Havelock Ellis, Stefan Zweig and H. G. Wells.

The letters stand as a stirring tribute to one of the most outstanding personalities of our times. They reveal a portrait of Sigmund Freud depicting the breadth of his nature, as his son says, the passion and single mindedness not only of a young man in love but of the mature man in his life-long search for scientific proof.

M.B.

Sea Within. The Story of Our Body Fluid. By WILLIAM D. SNIVELY, JR., M.D., University of Louisville School of Medicine. Pp. 150; 55 ills. Philadelphia and Montreal: J. B. Lippincott Company, 1960. Price, $3.95.

IN an easy to read, simplified style, the author discusses the regulation of body fluids, electrolytes, and acid base balance in health and many disease states in almost storybook fashion.

This book is intended primarily for laymen interested in scientific aspects of human life, and, for the most part, meets this purpose admirably. It should be useful as introductory reading to premedical students, first year medical students, and physicians who have little acquaintance with body fluids. I.G.

Biochemical Values in Clinical Medicine. By ROBERT DUNCAN EASTHAM, B.A. (CANTAB.), M.D. (CANTAB.), D.C.P., DIPL. PATH., Consulting Pathologist to the Frenchay/Cossham Group of Hospitals, Bristol, England. Pp. 144. Bristol: John Wright & Sons Ltd., 1960 (The Williams and Wilkins Co., Baltimore, U.S. Agents). Price, $3.75.

IN this convenient pocket-size volume, the author has brought together a large body of biochemical information that is of value in clinical medicine. Aside from the normal range for values in the respective tests, the findings in pathological states are indicated, and special points are emphasized. Key references are listed for most of the parameters discussed.

This form of treatment of laboratory data will be welcomed by many resident and practicing physicians. C.Z.

Praktische Blutlehre. By Prof. Dr. Viktor Schilling. 16th ed. Pp. 263; 87 ills., and 8 color plates. Jena: Gustav Fischer Verlag, 1959. Price, DM 15.

This is a practical guide to clinical hematology. Methodology, morphologic characteristics, and various points of diagnostic importance are concisely presented for the usual blood dyscrasias and blood parasites. The generous use of illustrative case material adds materially to the teaching value of this book.

Students and practitioners who read German will find this a precise and authoritative manual for the material covered. C.Z.

Treatment of Cardiovascular Emergencies. By Aldo A. Luisada, M.D., and Leslie M. Rosa, M.D., Division of Cardiology, Chicago Medical School and Mount Sinai Hospital. Pp. 122. New York: The Blakiston Division, McGraw-Hill Book Company, Inc., 1960. Price, $1.95.

The purpose of this small manual is to provide a convenient source of knowledge regarding treatment of cardiovascular emergencies. Although it is concerned mainly with therapy, there are also given some pertinent diagnostic and physiopathologic data. In the appendix, emergency drugs to be carried by the physician are listed. J.Z.

I Prescribe Laughter. By Thomas Richard Rees, M.D., Fellow of the American College of Surgeons. Pp. 111. New York: Vantage Press, Inc., 1960. Price, $2.75.

The author, who believes in smiles rather than frowns, prescribes laughter. He urges that people stop taking everything too seriously but to spice up the dark life with a little laughter and relaxation. The doctor believes, "A merry heart doeth good like medicine."

The book consists of assorted jokes, anecdotes and pithy side comments for bedside use. There is a chapter of original verse, referred to as "Safe-T-Tables," which deal with the problem of traffic accidents.

There are many cliches to be found in this little book. The author fails to deal with the inappropriateness of poorly timed humor or the care with which witicisms can be employed to inspire others. M.B.

Journal of Existential Psychiatry, Vol. 1 No. 1. Jordan M. Scher, M.D., Editor. Pp. 154. New York: Libra Publishers, Inc., 1960. Price, $8.00 per year, published quarterly.

In the prolegomena we read "Man is not merely the prisoner of mental mechanisms, diagnostic categories, primitive urges, or repetitions. He is capable of the unexpected as well as the expected. It is this order of thinking we must employ in attempting to understand, much less treat, the individual patient."

There are 10 contributions in this first journal of Existential Psychiatry. The journal will appeal to those interested in or wishing to learn more about this philosophy of pessimistic activism. M.B.

The Roots of Crime. By Edward Glover, M.D., LL.D. Pp. 422. New York: International Universities Press, Inc., 1960. Price, $7.50.

This volume contains a collection of Dr. Glover's contributions in the field of delinquency and crime covering a period of 37 years. The subject matter is approached from the psychoanalytic point of view and covers the diagnosis, treatment and prevention as well as the social and legal aspects of crime.

The author's extensive clinical experiences in this field, which qualify him as an expert, are placed in the perspective of his understanding of the dynamics and motivation of human behavior. Dr. Glover's views which are clearly stated are recommended as worthy of the attention of all students of human behavior. W.R.

Basic Theory of Psychoanalysis. By Robert Waelder, Chairman, Educational Committee of the Institute of the Philadelphia Association for Psychoanalysis. Pp. 273. New York: International Universities Press, Inc., 1960. Price, $5.00.

Basic Theory of Psychoanalysis is an outstanding contribution to analytic knowledge. Its value is enhanced since the basic concepts are discussed within a framework of the historical development of psychoanalysis.

Dr. Waelder brilliantly clarifies misunderstandings concerning psychoanalysis, but at times his style of writing is defensive as in his comparison between the "American" and "European" psychoanalyst.

This book is packed full of information, presented in an interesting and often amusing style. It will appeal to all groups of readers; to those highly informed or not well informed about psychoanalysis. M.B.

Heredity and Human Nature. By David C. Rife, International Cooperation Administration. Pp. 265; 34 ills. New York: Vantage Press, 1960. Price, $4.50.

The author, a former professor of Genetics at Ohio State University and now with the International Cooperation Administration in Thailand, has written a book in which he emphasizes the importance of genetic factors as an underlying cause for differences in human behavior. Sociologists would disagree strongly with much that he attributes to genetic rather than environmental influences. The book is written for the layman and most of it is devoted to presenting basic genetic principles in terms understandable to one with no previous exposure to this science. B.C.

Psychoanalysis and Moral Values. By Heinz Hartmann, M.D., Honorary President, International Psychoanalytic Association.

Pp. 121. New York; International Universities Press, Inc., 1960. Price, $3.00.

THE author outlines the contribution of psychoanalysis to the understanding of moral values. The significance of self-knowledge to moral ideals is discussed. Psychoanalysis in itself cannot provide the individual with the ultimate ends for the moral aspects of his personal, social or political behavior. The moral value of the psychoanalyst may be reflected in his treatment.

This little book is a valuable contribution to the subject. The grammatical construction is difficult at times and the book is not always easy to read. M.B.

Surface and Radiological Anatomy for Students and General Practitioners. BY W. J. HAMILTON, M.D., D.Sc., F.R.S.E., Professor of Anatomy, University of London, and G. SIMON, M.D., B.CH., D.M.R.E. (CANTAB.), F.F.R., Demonstrator of Radiological Anatomy in the Medical College of St Bartholomew's Hospital. 4th ed. Pp. 355; 416 ills. Baltimore: The Williams & Wilkins Co., 1958. Price, $9.50.

THE aim of this text has been "to provide an introduction to the study of features which are accessible to examination in the living subject." To older methods of physical examination roentgenologic visualization has been added in a correlation which is logical, both from practical and academic considerations. The result is a useful introduction to this important correlation that should interest medical students and radiology technicians. It should be emphasized that if the anatomy here is "surface" the radiology remains "superficial." H.S.

Radiopaque Diagnostic Agents. (Ann. New York Acad. Sci., Vol. 78, Art. 3). BY MAXWELL H. POPPEL AND 49 OTHERS. Pp. 315; illustrated. New York: New York Acad. Sci., 1959.

THIS volume presents the papers given at the Conference on the subject held at the New York Academy of Sciences, October 24 and 25, 1958. There are brief general considerations of the chemistry and pharmacology of the contrast agents useful in Roentgen diagnosis, chiefly the iodine-containing organic products. Papers follow dealing with specific new agents, some in clinical use and others only of experimental interest at present. There are also discussions of specific techniques of Roentgen "opacification," that is, lymphangiography, liver opacification, pancreatography and intravenous aortography. This is the best available summary of the present status of this field. H.S.

Roentgenologic Diagnosis in Ophthalmology. BY EDWARD HARTMANN, M.D., Chief of the Ophthalmic Department, Larboisiere Hospital and American Hospital in Paris, and EVELYN GILLES, M.D., Chief of the Roentgenology Department, Quinze-Vingt Ophthalmic Hospital, Paris. Translated by GEORGE Z. CARTER, M.D., Assistant Professor of Ophthalmology, Albert Einstein College of Medicine. Edited by CONRAD BERENS, M.D., Lecturer on Ophthalmology, New York University Post-Graduate Medical School. Pp. 375; 497 ills. Philadelphia: J. B. Lippincott Co., 1959. Price, $15.00.

THIS collaborative effort is unique in its field. The treatment of problems involving the orbit, the sella turcica and the lacrimal passages is particularly good. Roentgenologic techniques are outlined, illustrations of roentgenograms are satisfactory, and the text is terse. Portions of the skull and its contents other than those mentioned are given only cursory consideration. H.S.

Acta de L'Institut D' Anesthésiologie, Vol. 8, 1959, Cours Supérieur D'Anesthésie. Edited by PROFS. P. MOULONGUET AND J. BAUMANN. Pp. 277; illustrated. Paris: Librairie Arnette, 1959.

THIS is the eighth in a series of paper-bound volumes dedicated to postgraduate instruction in anesthesiology. It consists of a collection of lectures and papers on subjects of current interest in the field, such as anesthesia of ambulatory patients; the dead space and the elimination of carbon dioxide; induced cardiac arrest; the treatment of barbiturate coma; ammoniacal intoxication and liver coma; the treatment of tetanus, and others. R.K.

Fourth Tissue Homotransplantation Conference. BY JOHN M. CONVERSE AND BLAIR O. ROGERS AND 101 OTHERS. (Ann. New York Acad. Sci., Vol. 87, Art. 1.) Pp. 607; illustrated. New York: New York Academy of Sciences, 1960. Price, $5.00.

THIS is a valuable record and summary of current knowledge in a rapidly growing field: tissue homotransplantation. The papers are grouped under the headings Immunogenetics and Phylogenetics, Variations in the Response to Tissue Transplants, Antigen-Antibody Manifestations in Tissue Transplantation, Graft Versus Host Reactions and Immunological Tolerance and Organ Transplantation. The contributors are the leading workers in the field. R.K.

The Home Encyclopedia of Modern Surgery. BY JAMES HALE RUTLEDGE, B.S., M.D., F.A.C.S., a practicing surgeon in Taylorsville, Illinois. Pp. 295; 140 ills. Philadelphia and New York: Chilton Company, Book Division, 1960. Price, $8.00.

THE cover entitles this book The Concise Encyclopedia of Modern Surgery and indicates that it might be useful for medical students, interns and nurses. This is misleading for there could be nothing further from the fact on this. Actually the title of the book as listed The Home Encyclopedia of Modern Surgery, I think most adequately characterizes this book. The only question that one might raise about it is whether or not there is too much material here for home consumption.

However, from the point of view of the lay public, I think this book has been well done. R.T.

Peptic Ulceration. By CHARLES WELLS, Professor of Surgery, The University of Liverpool and JAMES KYLE, M.B., M.Ch., F.R.C.S., F.R.C.S.(I.), Senior Lecturer in Surgery, University of Aberdeen. Pp. 249; 40 ills. Edinburgh and London: E. & S. Livingstone Ltd., 1960. (The Williams & Wilkins Co., Baltimore, U.S. Agents.) Price, $8.75.

THIS well written book is to be highly recommended for the student of peptic ulcer disease. The authors are to be commended for the concise, clear statement that is present and also for the excellent organization and coverage of the material. R.T.

Bibliography on Bilharziasis, 1949-1958. Pp. 158. Geneva: World Health Organization, 1960. Price, $2.00.

Connective Tissue and Diseases of Connective Tissue (Ann. New York Acad. Sci., Vol. 86, Art. 4). By BERNARD M. WAGNER AND 41 OTHERS. Pp. 254; illustrated. New York: New York Academy of Sciences, 1960. Price, $3.50.

THIS is a paper-bound record of the New York Academy conference on connective tissues held in January, 1960. It consists of 19 papers which review the most recent research material dealing with the physiology of the connective tissues, especially in relation to hypersensitivity. It presents a quick review of this particular research frontier by some of the best workers in the field. E.A.

Symposium on Congestive Heart Failure. Edited by HERRMAN L. BLUMGART, M.D., Professor of Medicine, Harvard Medical School. Monograph No. 1. Pp. 120; 21 ills. New York: The American Heart Association, Inc., 1960. Price, $2.00.

IN *Circulation*, the official journal of the American Heart Association, there have appeared in the monthly issues reviews of various aspects of the cardiovascular system. These reviews are authoritative and timely. Pertinent material is organized and interpreted in the light of the experience of a distinguished investigator. To permit convenient continuity and wider dissemination, it apparently is the plan of the American Heart Association to publish related reviews in monographic form. This one, the first, concerns itself with congestive heart failure and contains 11 such reviews, beginning with that of Starling's concept of heart failure by Sir George Pickering and ending with that of rehabilitation by Doctors Rusk and Gertler. Between these, there are presentations of the fundamental aspects of heart failure, its cause and treatment, be it in lung disease, pediatrics or pregnancy. Dr. Blumgart, the editor, has his fingers on the pulses of his readers and continues to anticipate the need for new and inspiring ways in which a journal may best serve its function. Having done so, the American Heart Association is to be commended for its efforts to bring this material to us, to keep us informed and knowledgeable. J.Z.

Pressure Group Politics: The Case of the British Medical Assocation. By HARRY ECKSTEIN, PH.D., Princeton University. Pp. 168. California: Stanford University Press, 1960. Price, $3.75.

THIS book, by an American social scientist, follows the author's previous study of *The English Health Service*. It analyzes the structure of the British Medical Association and its public relations, recent negotiations between the B.M.A. and the Ministry of Health, and the political setting in which these groups operate.

The role of "pressure groups" in democratic systems is examined, in Britain and the United States. The differences in governmental systems do not make one country's plan applicable to the other, yet democratic threads in each political fabric are often similar. This carefully prepared study, by a member of the Department of Politics and Center of International Studies at Princeton, makes timely and thought-provoking reading. F.R.

Diabetic Care in Pictures. By HELEN ROSENTHAL, B.S. AND JOSEPH ROSENTHAL, M.D., Assistant Professor of Medicine, Tufts University. 3rd ed., Pp. 237; 137 ills. Philadelphia: J. B. Lippincott Co., 1960. Price, $4.50.

THIS well-known useful volume for diabetic patients has been thoroughly revised in its third edition. Physicians not familiar with the style of presentation employed by the authors should inspect this latest effort. Particular attention is given to the problem of dietetics reflecting the origin of the book in the renown Frances Stern Food Clinic and Diabetic Clinic of The Boston Dispensary. The visual aid method used throughout portrays for the patient the specific foods, sizes of portions and the role they play in nutrition. The total care of the patient is effectively presented in this graphic form providing a readily understood treatment program for the reader. C.S.

British Medical Bulletin: Insulin. Edited by F. G. YOUNG, M.D., Professor of Biochemistry, University of Cambridge. Volume 16, Number 3. Pp. 89; 17 ills. London: Medical Department, The British Council, September, 1960. Price, $3.25.

THIS volume encompasses most of the important information concerning insulin and insulin substitutes available to physicians at the present time. Among its contributors are listed some of the foremost authorities whose work has laid the guide-lines in this field. Professor C. H. Best re-explores for the reader the early researches leading to the discovery of the hormone and

its subsequent development. Dr. Sanger reports the details of his investigation of the chemical structure of the insulin molecule together with recent studies on insulin derived from the human pancreas. One recalls that Sanger received the Nobel Prize for Chemistry in 1958 for his brilliant work in this field. The biological activity of insulin, methods of assay and standardization of the hormone are subjected to detailed examination. A variety of insulin antagonists, including antibody to insulin, have been demonstrated in recent years which merit urgent consideration. These factors are identified and described by Vallence-Owen and Wright in relationship to their significance in the insulin-deficient syndrome. The influence of insulin in protein metabolism and lipogenesis is now fully appreciated; whether these effects can be explained in terms of a single action of the hormone remains uncertain according to Randle and Young in their discussion of insulin mechanisms. The clinical uses of insulin and insulin substitutes are described respectively by Oakley and Nabarro in the concluding section of the volume. C.S.

A Polychrome Atlas of the Brain Stem. By WENDELL J. S. KRIEG, Professor of Anatomy, Northwestern University Medical School. Pp. 5 single, 11 folio; plastic ring binder; 10 ills. monochrome, 10 ills. polychrome, 1 summary chart. Evanston, Ill.: Brain Books, Book Nine, 1960. Price, $3.00.

THAT gaps exist in a student's grasp of neuroanatomy is well known to experienced teachers in this discipline. Professor Krieg has graphically pointed up an area of frequent confusion and frustration for a beginner studying the brain.

The effective clarity of the blue monochrome figures lies in their dignified simplicity; the impressiveness of generous sized, beautifully reproduced polychrome hemisection figures is achieved through the skillful blending of many structures, many colors, many labels. This atlas is another artistic expression of Professor Krieg's sincere efforts towards a more lucid portrayal of the nervous system and a desire for greater facilitation in the learning process; it should assist the student towards a useful orientation of the morphology of the medulla oblongata, pons and mesencephalon. J.B.

L'Âge Atomique et Notre Avenir Biologique. By H. V. BRONSTED. Pp. 90. Paris: Masson et Cie, 1959. Price, 850 fr.

THE small English volume in which the author dealt with the biologic aspects of atomic radiations in simple terms has now been translated into French. Thus information in this fundamental area becomes available to another large segment of the world population. C.Z.

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